Examining the evidence for a psycho-physiological model of Chronic Fatigue Syndrome in adolescents

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August 2014

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Acknowledgements

This thesis would not have been possible without my PhD supervisors, Professor Trudie Chalder and Dr Katharine Rimes. Your vast knowledge of the area, expertise and experience, combined with support and encouragement has been an inspiration and has fuelled my desire to pursue a career in psychological research. I also acknowledge the financial support from the Biomedical Research Council who funded the project.

Thank you also to the Biostatistics department for statistical advice and to James, Hannah, Fatma and Egli for the video coding. I would also thank to thank everyone at the Chronic Fatigue Syndrome Research and Treatment Unit and the CFS team at Great Ormond Street Hospital for helping with recruitment of participants and again for your continued support and encouragement. Extended thanks to the other researchers at the CFS Unit for such positivity throughout.

The GP surgeries that permitted recruitment of the asthma patients from their surgeries and schools aiding the recruitment of healthy controls were vital in this thesis. I offer a thank you to them as they made the process possible.

I am very grateful to those participants who took part in the study. It was a commitment of time that I will always be thankful of. It was a pleasure working with each and every family.

Lastly, I would like to give a huge thank you to my friends and family for always believing in me and for their endless love, support and guidance. Specifically, thank you to my parents and sister for their lifetime of encouragement in pursuit of this career in psychological research. To Tom, you have been such a support throughout the PhD, particularly over recent months when I have been writing up, I couldn't have done it without you.

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Abstract

Introduction. The purpose of this thesis is to investigate the factors associated with predisposing, precipitating and perpetuating fatigue and disability in Chronic Fatigue Syndrome in adolescents. It presents novel evidence of psychological (including behavioural), social and physiological factors associated with adolescent Chronic Fatigue Syndrome.

Methodology. In order to test a hypothesised psycho-physiological model of Chronic Fatigue Syndrome in adolescents, a cross-sectional and prospective case-control design was used. Eighty-five adolescents with Chronic Fatigue Syndrome, thirty-one adolescents with asthma and seventy-eight healthy control adolescents participated in the study. They were compared on a range of questionnaire measures at two time points. Experimental tasks were also used to test hypothesised maintaining factors for Chronic Fatigue Syndrome in adolescents derived from cognitive behavioural approaches. Physiological parameters were assessed during these tasks. Mothers of all adolescents completed questionnaire measures examining maternal distress and other psychological variables.

Results. The Chronic Fatigue Syndrome group and their mothers scored significantly higher on all measures of unhelpful beliefs and behaviours in response to illness than the asthma group. Maternal distress and worse general health were also more common in the mothers of adolescents with Chronic Fatigue Syndrome. The adolescents and their parents had lower expectations of performance on the experimental tasks than the other two groups, most prominently on the exercise task. The Chronic Fatigue Syndrome group were more likely to attribute cognitive symptoms of stress to their illness rather than the stress of a speech task in comparison to the adolescents with

asthma. The Chronic Fatigue Syndrome group had a significantly higher Heart Rate in anticipation of the speech and the exercise task as well as slower Heart Rate recovery compared to the other groups. The Chronic Fatigue Syndrome patients also had significantly lower Heart Rate Variability and higher Skin Conductance Response at baseline compared with the other two groups.

Conclusions. This thesis confirms that cognitive, behavioural, emotional and social factors are associated with Chronic Fatigue Syndrome in adolescents. Some of these factors will need to be targeted in treatment. The differences between groups on physiological responses are consistent with the hypothesis that adolescents with Chronic Fatigue Syndrome may differ in their autonomic response to challenging situations. In particular they appear aroused in anticipation of exercise and recover more slowly from a stressful situation. The findings support the use of cognitive behavioural intervention methods in which the family is involved in assessment and treatment (Chalder *et al.*, 2002).

Chapter 1: Introduction

Synopsis

Chronic Fatigue Syndrome (CFS) is a condition characterised by severe mental and physical fatigue coupled with profound disability. The purpose of this thesis is to investigate the factors associated with predisposing, precipitating and perpetuating fatigue and disability in CFS in adolescents. Chapter 1 sets the context of this thesis, providing an overview of the psychological, social and physiological factors associated with fatigue and disability in CFS in adolescents. It describes the literature review (Lievesley *et al.*, 2014) that was conducted to gain an overview of the strength of evidence for the relationship between these different factors and CFS in adolescents. Clinical implications of the findings and current treatment models are discussed. A hypothesised model of the factors associated with CFS in adolescents is presented. Finally, the rationale, aims and hypotheses of the thesis are presented.

Overview of CFS

Chronic Fatigue Syndrome (CFS) is a condition characterised by severe mental and physical fatigue that is not alleviated by rest, coupled with significant disability. This thesis focuses on children and adolescents with CFS (11-18 years). Sometimes called Myalgic Encephalomyelitis (ME), it can be associated with a variety of physical complaints such as muscle pain, headache, sore throat and increased somnolence (Marshall *et al.*, 1991). Petrov *et al.* (2011) reported that other than fatigue, headaches and sleep disturbance are the most common symptoms in young people with CFS.

Diagnosis

For a diagnosis of CFS, fatigue must be the principal symptom, of definite onset and disabling, affecting both physical and mental functioning. According to the Oxford criteria, CFS is defined as self-reported persistent or relapsing fatigue lasting six or more consecutive months, for at least 50% of the time (Sharpe *et al.*, 1991). Appropriate clinical tests are undertaken to rule out any medical conditions known to result in chronic fatigue.

Patients are excluded if diagnosed with current schizophrenia, substance abuse or proven organic brain disease. However, anxiety and depressive disorders are not necessarily reasons for exclusion. The Fukuda criteria (Fukuda *et al.*, 1994) states that the criteria for severity of fatigue must be met, as well as four or more of the following symptoms being concurrently present for 6 months; 1) impaired memory or concentration 2) sore throat 3) tender cervical or sore lymph nodes 4) muscle pain 5) multi-joint pain 6) new headaches 7) un-refreshing sleep and 8) post-exertion malaise. The Fukuda case definition was devised primarily for adults with CFS. A child and adolescent focused definition has since been proposed (Jason *et al.*, 2006). As with the adult criteria, a thorough patient history is taken along with ruling out any other possible diagnoses. The authors emphasise a need to involve the parents in this process. A key difference to the adult definition is that the authors removed the necessity for a definite onset as it may not be possible for the young person to pinpoint an exact onset for their fatigue.

In adults, the criterion duration is 6 months. For children, researchers and clinicians recognised the need for children to be diagnosed as quickly as possible at a crucial time of their development so the diagnosis can be made after three months (Jason *et al.*,

2006). UK clinical guidelines state that this diagnosis should be made or confirmed by a paediatrician (NICE, 2007).

Prevalence

Prevalence is the total number of cases of a condition in a given population at a specific time. In two community studies where CFS was confirmed by a paediatrian (Bell *et al.*, 1991; Jordan *et al.*, 1998), the prevalence of CFS was estimated at about 2% in 6-17 year olds. Bell et al. (1991) assumed all non-responders (353 out of 914) were asymptomatic so the prevalence was an extrapolated prevalence (2.3%). The study was carried out prior to the Fukuda criteria (Fukuda *et al.*, 1994), but they retrospectively checked that the patients had > 6months fatigue and 6 of 8 symptoms for CFS as outlined in Holmes et al. (1988). However, other studies have found lower prevalence rates. In a large, epidemiological population study in the UK (England, Scotland and Wales), the prevalence of CFS in children and adolescents (5-15 year olds) was 0.19%, comparable to the rate found in less common childhood disorders such as severe tic disorders or eating disorders (Chalder *et al.*, 2003). Another well-conducted community based study in the US (Jordan *et al.*, 2006) found a prevalence rate of 0.18% in 13 to 17 year olds. However, in another population based study in the US (Jones *et al.*, 2004), no CFS case was identified (N=8586). This was a random digit dialling survey in Kansas, where parents identified fatigued children and adolescents in their home. Using questionnaires sent to General practitioners (GPs) in a nationwide study in Holland, Nijhof et al. (2011) reported that 111 per 100000 young people (10-18 years old) had CFS. GPs were questioned about practice size and the number of CFS diagnoses. It is possible that the number reported was under-represented as GPs may have overlooked

some patients and other young people may have been receiving treatment in tertiary care only. Using a three month minimum symptom duration, Farmer et al. (2004) observed that the lifetime prevalence for CFS in young people was 1.90%, based on 96 young people (8-17years) from population based registers in South Wales and Manchester. All of these studies used the Fukuda criteria for diagnoses (Fukuda *et al.*, 1994).

Incidence

Incidence is a measure of the risk of developing some new condition within a specified period of time; i.e. the number of "new cases" in a population within a given time period. A UK epidemiological study (Rimes *et al.*, 2007) found an incidence of CFS of approximately 5 per 1000 over a 4-6 month period - using the Fukuda criteria (Fukuda *et al.*, 1994). That is higher than that of asthma, type 1 diabetes or anxiety disorders for this age-group (5-15 year olds). These findings broadly compare to the incidence figures reported in the adult population (Lawrie *et al.*, 1997). However, Nijhof *et al.* (2011) in the same study discussed above reported an incidence rate of 12 per 100000 per year. This was calculated from newly reported cases by paediatricians in 2008. Paediatricians were sent a questionnaire every time a new diagnosis was made. They captured patient's demographic details as well as information about duration and severity of fatigue. Crawley *et al.* (2011) conducted a school based project investigating CFS in young people aged 11-16 years using the broader 3 month duration for young people as recommended by the NICE guidelines (NICE, 2007). They gathered data on newly diagnosed CFS cases. A school attendance service in conjunction with a specialist CFS service identified young people missing greater than 20% of school and those with

fatigue were referred to a specialist unit. Twenty-eight of the 2855 (1%) young people from the 3 state secondary schools the service was offered in were found to have CFS. The considerable variation in methodology and age-range in these studies is likely to account for some of the differences in incidence estimates.

Adolescence

This stage of development is very diverse but is widely considered to begin from about the age of 11. The prevalence evidence suggests that CFS-like illness is unusual before puberty. Jordan *et al.* (2000) reported a prevalence of 2.91% in adolescents and only 1% in pre-pubescent children. Key changes in adolescence are the hormonal and biological changes along with sexual maturation and the development of one's own personal identity. Adolescence is described as a period in which independence is achieved. It is a time when constancy in certain characteristics such as personality and behaviour develop. The adolescent process of individuation and separation from parents can be impeded by the increased dependency which is often associated with CFS.

Gender

CFS is more common in females than males in children and adolescents (Farmer *et al.*, 2004) as well as adults (Gallagher *et al.*, 2004). The ratio is approximately 3:1 for children and young people in prevalence studies (Farmer *et al.*, 2004). Buchwald *et al.* (2000) reported that female sex was a risk factor for non-recovery from infection mononucleosis at 6 months in adults. It is possible that sex hormones play a part in this disparity. Hormones, such as testosterone and oestrogen are known to profoundly

impact on the central nervous system, which is responsible for perceiving and transmitting the feeling of pain (Bialek *et al.,* 2004). Testosterone has been shown to help prevent muscle fatigue through helping to repair muscles after activity (Axell *et al.*, 2006). It is possible given that women have less testosterone that they are prone to more muscle fatigue. However there is no evidence about hormonal differences contributing to the gender difference in CFS prevalence rates.

For some adults with CFS there is evidence of mild hypocortisolism, and this is more common in women with CFS than men (Papadopolous & Cleare, 2012). Reasons for this hypocortisolism are unclear but one suggestion from the adult CFS literature is that it is a consequence of childhood trauma (Heim *et al.,* 2009). Childhood abuse and stressors are discussed later in the review. A meta-analysis study reported a global prevalence of childhood sexual abuse as 19.7% for females and 7.9% for males (Pereda *et al.,* 2009). It is widely accepted that those individuals who have reported childhood abuse are more likely to also suffer with depression and anxiety issues as well as more physical symptoms (Arnow, 2004). Again, these conditions are more common in females than males and have overlapping symptoms with CFS.

Ethnicity

Data on ethnicity in CFS in adolescents is limited. Dinos *et al.* (2009) reported through a narrative synthesis and a meta-analysis of population based studies (e.g. (Jason *et al.*, 1999a)) in the USA, a higher prevalence of CFS in some ethnic minority groups than white people in adults. However, ethnic groupings can be arbitrary in studies so it can be difficult to gain accurate prevalence rates. Studies in secondary or tertiary care report relatively low percentages of non-white patients in adults with CFS (Jason *et al.*, 2003;

Luthra & Wessely, 2004). These findings raise questions about selection bias in care settings and why those from diverse ethnic groups may not get a CFS diagnosis or be referred to specialist services. Results from population based studies give a less biased picture of the relationship between CFS and ethnicity.

Clinical Picture

Heterogeneity

There is some evidence that CFS in young people is a heterogeneous condition. May, Emond & Crawley (2009) undertook a factor analysis of items endorsed on a symptom checklist by young people with CFS and reported three different phenotypes. They labelled these "musculoskeletal" (e.g. muscle pain, joint pain), "migraine" (which included headache, abdominal pain and hypersensitivity to noise, light and touch) and "sore throat" (characterised by sore throats and swollen lymph nodes). The authors reported that worse fatigue, pain and physical function were cross-sectionally associated with musculoskeletal and migraine phenotypes. In this type of study the phenotypes identified will depend on the list of symptoms chosen by the researcher. Studies in the adult literature (Nisenbaum *et al.*, 2004; Wilson *et al.*, 2001) do support the notion that the presentation of CFS is heterogeneous.

Neuropsychological Symptoms

There has been little research carried out on the different symptoms of CFS in children and adolescents. However, problems with memory and attention in young people with CFS have been examined. One study found that one third of child and adolescent

patients with CFS reported a decrease in concentration. Patients described feeling like they were in a 'fog' (Krilov *et al.*, 1998). Problems with attention - specifically attending to external cues, such as conversations or instructions - were reported by parents, teachers and the young people alike in an uncontrolled, cross-sectional study, using a population of young people with CFS who reported problems with memory or concentration (Haig-Ferguson *et al.*, 2009). In comparison to normative means, Haig-Ferguson et al. reported significantly lower scores for the young people with CFS on sustained attention, switching attention, divided attention, immediate recall and delayed recall when using a neuropsychological assessment. This is in line with subjective reports. However, van Middendorp *et al.* (2001) found normal adjustment on attention problems in young people with CFS, using self-report measures.

A cross-sectional study (van de Putte *et al.*, 2008) used a flanker task (Eriksen Flanker Task, EFT(Eriksen & Eriksen, 1974)) to specifically investigate whether young people with CFS were easily distracted. A flanker task is a test of response inhibition. It requires a participant to suppress inappropriate responses in a given context. In this study, the participants had to respond to a target which was flanked by non-target stimuli which acted as distractors. Such tasks are widely used to measure attention and distractability. The CFS group performed significantly worse on the Erikson flanker task than the healthy control group, with slower reaction time and less accurate performance. This finding of greater distractibility is supported by findings in the adult literature (DeLuca *et al.*, 1997). A further cross-sectional study using the modified Trail Making Task reported that the young people (13-15 years old) with CFS showed significantly slower alternative attention than the healthy control group (Kawatani *et al.*, 2011). These problems may account for some of the educational difficulties reported in CFS (Sankey *et al.*, 2006).

Disability

Symptoms of fatigue are often exacerbated by activity, with the young person being left with days of feeling unwell afterwards. The disability associated with CFS can vary considerably. At the more severe end, children and young people are unable to go to school (Sankey *et al.*, 2006). Crawley and Sterne (2009) investigated school attendance and physical function in 211 children and adolescents (5-19 year olds) with CFS. They found that 62% attended school 40% or less. The factor most strongly associated with lower school attendance was lower physical functioning. Increased fatigue, pain and low mood were associated with worse physical function. Based on the case notes of 50 young people attending one of two London Tertiary paediatric / psychiatric centres over the previous 5 years Rangel *et al.* (2000b) reported that 57% were bedbound when functional handicap was at its worst, with a serious reduction in physical activity.

Theoretical underpinnings to clinical treatment

Cognitive behavioural therapy is the only psychological treatment that has been empirically investigated using randomised controlled trials in CFS (Chalder *et al.*, 2010; Stulemeijer *et al., 2005*). It is the recommended treatment option in the UK (NICE, 2007). Stulemeijer *et al.* (*2005*) found that patients given a course of cognitive behavioural therapy over a 5 month period reported a significantly greater decrease in fatigue severity, functional impairment and their attendance at school improved significantly, as compared to a waiting-list control group. These benefits of CBT were consistent with the findings by Chalder *et al.* (2010).

Theories informing such therapeutic options for young people with CFS have been broadly based on models and research evidence in adults. Wessely *et al.* (1989)

suggested that although fatigue may often have been initially triggered by an infection, other factors may then act to maintain the condition. They propose that the individual starts to reduce their activity levels in an understandable attempt to feel less fatigued, but in fact their exercise tolerance worsens and hence fatigue increases when they try to do more. Beliefs such as "There must be something seriously wrong with me" and "If I continue with this activity I will end up feeling worse", contribute to activity reduction and avoidance. They suggest that the individual ends up in a vicious cycle of activity reduction, exercise intolerance, fearful cognitions, fatigue and disability. This has led to cognitive behavioural interventions addressing such factors. Surawy *et al.* (1995) built on this initial model, developing a more cognitive-based theory which captures these important maintaining factors as well as other cognitive factors including high personal standards and self-expectations. For young people, Chalder, Tong & Deary (2002) suggested that treatment be delivered within the context of the family as they can be influential in the development and maintenance of the condition. However, this is far from clear, as so far family-based approaches have not been compared to one-to-one treatment in this condition.

Literature Review - overview

This review aims to document the research studies which have investigated biological, psychological and social factors which may be contributing to either the aetiology or maintenance of adolescent CFS. This will include a review of factors for which there is research evidence for in adults with CFS or which have been proposed in previous theoretical approaches, including immunological functioning, infection, activity / rest, and cognitive factors. At the end of the review a multifactorial model of hypothesised

factors in children and adolescents with CFS is proposed, drawing on the evidence from this review and the models of CFS already established.

Search method

Electronic databases (Medline, Embase, Psycinfo) were searched for published studies between 1980 and December 2013 on Chronic Fatigue Syndrome in children and adolescents. Key search words were; Chronic Fatigue Syndrome AND genetic, personality, self-esteem, cortisol, stress, activity, exercise, infection, physiol*, arousal, belief, depression or anxiety, psychol*, autonomic or cardiovascular. Additional search terms included adolescent or child* or young person or young people or juvenile. Studies were included if they addressed factor(s) associated with CFS in children and adolescents. Intervention studies were not included in this review. Some studies (n = 7) came from trawling through reference lists of identified papers. The search strategy identified 79 studies to be included. Information about study design, sample characteristics, measures used and main findings was extracted from the articles and tabulated (see table 1.1). Due to such a broad research question, as well as heterogeneity of studies, a narrative approach to this review has been taken. Factors were grouped into categories and then a mini-review of each category was conducted. Both similarities and differences across the studies were explored for issues such as methodology and sample size. This led to an overview of the nature and strength of evidence as well as directions for future research.

Table 1.1: Studies investigating the factors associated with chronic fatigue syndrome in adolescents

Factor		**Methodology**		**Total**	**Case-Control?**		**N**		
		Cross-sectional	**Prospective**	**Total**	**Yes**	**No**	**<50**	**50-100**	**>100**
Predisposing and perpetuating factors	Genetics	7	0	7	2	5	2	3	2
	Psychiatric disorder	20	0	20	6	4	8	8	4
	Personality	4	1	5	3	2	4	1	0
	Self-esteem	6	0	6	4	2	5	1	0
	High expectations	3	0	3	3	0	2	1	0
	Attributions	6	0	6	2	4	5	1	0
	Illness perceptions and cognitions	5	0	5	4	1	3	2	0
	Parental involvement – maternal distress	5	0	5	3	2	1	2	2
	Parental care and over-protection	4	0	4	3	1	2	2	0
	Endocrine factors	14	2	16	15	1	14	2	0
	Activity levels	3	0	3	0	4	3	0	1
	Sleep	0	1	1	1	0	1	0	0
	Body mass index (BMI)	1	0	1	0	1	0	1	0
Precipitating	Infection	10	1	11	3	8	6	3	2

Results

Overview

Most of the 79 studies identified were cross-sectional (N=66). Two studies were prospective. Forty-one studies were case-control studies. Most often, self-report measures were used to measure the factors. Most sample sizes ranged between 5 and 100 (N = 58). However, some were population-based studies using a much larger sample. Most studies used an age range between 11 and 25 years. Only 6 studies used a sample over 25 years of age. These are the studies looking at factors in childhood influencing a diagnosis in adulthood. Four papers included participants less than 11 years of age. This thesis addresses CFS in young people generally, but the majority of studies concentrate on the stage of adolescent development (11-18 years) and that is subsequently the main focus of this review and thesis. All studies included both males and females in their sample other than one study (ter Wolbeek *et al.*, 2007). Ethnicity is not widely reported in studies investigating CFS in young people.

Thirty-eight of the studies investigated psychiatric adjustment within CFS samples as one of their outcomes, with the main disorders measured being anxiety and depression. In these studies, analyses were primarily regression or correlation analyses.

The results are considered beneath two key headings (table 1.1 shows the studies separated by factors):

- predisposing / vulnerability factors (may also act as perpetuating factors)
- precipitating factors

It should be noted that some factors could potentially act in more than one category. For example, a particular personality characteristic might put an adolescent at risk for

developing CFS and also act to maintain it once it has developed. Due to the cross-sectional nature of studies, these are reported under one heading.

Predisposing / Vulnerability factors (may also act as perpetuating factors)

Genetic and familial factors

Five cross-sectional studies (Bell *et al.*, 1994; Bell *et al.*, 1991; Crawley & Sterne, 2009; Patel *et al.*, 2003; Smith *et al.*, 2010) have reported a link between a family history of CFS and developing CFS in young people. Bell *et al.* (1991) found that having a family member with symptoms of CFS was a strong predictor of CFS in students in a district in New York, with a risk ratio of 35.9. Further, 50% of young people with CFS referred to a Paediatrics department had a family history of CFS (Bell *et al.*, 1994). Patel *et al.* (2003) found 13.9% (of 36) at a GP special interest clinic had a positive family history of CFS in a first degree relative. Crawley and Sterne (2009) report 20% of 211 young people with CFS recruited from a regional specialist survey had a first degree relative who had CFS. In comparison with offspring of healthy mothers (n=30), Smith *et al.* (2010) found that those exposed to mothers with CFS (n=20) met criteria for CFS more frequently (12% vs. 2%). There was only low to medium power to detect a significant difference. The authors recruited mothers with CFS from an academic referral clinic devoted to chronic fatigue and pain and all offspring had been living with their mother continuously (at least since the age of 12).

There is one study using twins to investigate genetic heritability of chronic fatigue in young people (Farmer *et al.*, 1999). Investigating disabling fatigue in school aged twins, the genetic contribution was high, with a mono-zygotic (MZ) correlation of 0.75 and di-

zygotic (DZ) correlation of 0.47, for fatigue lasting at least a month (Farmer *et al.*, 1999).

Sommerfeldt *et al.* (2011) studied 53 patients with CFS (12-18 years) and found significant differences in genotype frequencies between the CFS group and reference samples. Specifically, they found differences on the COMT SNP Rs 4680 and the β2 adrenergic receptor SNP Rs 1042714. The most significant finding was the high frequency of the AA genotype. These receptors are associated with enzyme activity. Attentuation of enzyme activity leads to an increased concentration of catecholamines, possibly intensifying the effect of sympathetic nervous activity. This ties in with the Wyller et al. (Wyller *et al.*, 2008; Wyller *et al.*, 2007b; Wyller *et al.*, 2007c) findings discussed later (endocrine factors). These studies found abnormalities in immune functioning and inflammatory processes in young people with CFS in comparison to controls.

Psychiatric disorder

Authors have investigated the overlap and distinction between psychiatric disorders and CFS. Concurrent psychiatric disorders (mostly depressive disorders) are reported in between a quarter to a third of young people with CFS (community sample (Sharpe *et al.*, 1991); specialist treatment centre sample (Vereker, 1992); attending an immunology clinic for CFS (Walford *et al.*, 1993)). Case-control studies have specifically examined the number of patients with CFS presenting with psychiatric disorders compared to healthy norms (van Middendorp *et al.*, 2001) or healthy controls (Fry & Martin, 1996; Garralda *et al.*, 1999; Godfrey *et al.*, 2009; Heim *et al.*, 2009; Smith *et al.*, 2003; ter Wolbeek *et al.*, 2007; van de Putte *et al.*, 2008; Walford *et al.*, 1993) or illness controls

using different control groups; cystic fibrosis (Walford *et al.*, 1993), emotional disorders (Garralda & Rangel, 2005), cancer group of adolescent girls (Pelcovitz *et al.*, 1995), inflammatory bowel disease (IBD (Richards *et al.*, 2005)), migraine (Smith *et al.*, 2003), juvenile rheumatoid arthritis (JRA (Brace *et al.*, 2000)) and juvenile idiopathic arthritis (JIA (Rangel *et al.*, 2003)). These studies mainly focused on reports of anxiety and/or depression and will be summarised below.

In the cross-sectional studies comparing CFS patients with healthy controls/norms, scores for depression and anxiety were significantly elevated in the CFS groups. Ter Wolbeek *et al.* (2007) reported that CFS patients had increased depression, anxiety and somatic symptoms as compared to non-fatigued controls. Rangel *et al.* (2000b) reported 12% of the 25 young people with CFS reached the severity cut off for a major depressive disorder, as measured by a semi-structured interview. Unipolar depressive disorder is a common mental health problem in adolescents worldwide, with an estimated 1 year prevalence of 4-5% in mid-late adolescence (Costello *et al.*, 2005). Recently, Bould *et al.* (2013) reported that 29% of 542 young people (12-18 years) with CFS were also depressed. This was according to a score of > 9 on the depression subscale of the Hospital Anxiety and Depression Scale (HADS (Zigmond & Snaith, 1983)). Those young people with CFS who were also depressed had higher levels of disability, pain, fatigue and anxiety as well as worse school attendance than those free of co-morbid depression.

In a larger sample of young people with CFS (n=164), Crawley, Hunt and Stallard (2009) reported a significant association between the Spence Children's Anxiety Scale total score (SCAS; (Spence, 1998)) and levels of fatigue (Chalder Fatigue Questionnaire; (Chalder *et al.*, 1993)). Most common were separation anxiety and social

phobia which were strongly associated with gender; a significantly higher proportion of girls scored above the anxiety scale cut-off than normative controls. Fisher & Crawley (2012) extended this study with eleven of the participants. These were amongst those who scored above the 90th percentile cut-off on the SCAS separation anxiety and/or social phobia subscales. They conducted interviews with the young people (12-18years) either at home (n=10) or at the specialist clinic (n-11) and found the young people with CFS had 'increased emotionality' and were more worried about schoolwork (compared to before). They were also anxious about returning to school.

In comparison to young people with other illnesses, depression scores were significantly higher in many of the CFS groups (Pelcovitz *et al.*, 1995; Rangel *et al.*, 2003; Smith *et al.*, 2003; Walford *et al.*, 1993). Higher anxiety scores were significantly more common in the CFS group than the juvenile idiopathic arthritis group (Rangel *et al.*, 2003). Richards *et al.* (2005) reported 50% of the CFS group reached the threshold for emotional disorders which was higher than the inflammatory bowel disease control group (30%), but this did not reach statistical significance. Garralda & Rangel (2005) reported that although the CFS group had less psychiatric co-morbidity than the Emotional Disorders group, where psychological problems was the primary diagnosis, emotional disorders had been present in most of the CFS group (18 out of 27) in the previous year. On the whole, measured through different diagnostic techniques, these studies suggest that a sizeable proportion of patients with CFS have a psychiatric comorbidity, usually anxiety or depression. Yet, some clear differences have been shown between childhood and adolescent CFS and depressive disorder. Specifically an acute onset of symptoms is more likely to be reported in patients with CFS compared to those with depression (in a sample of 16, 16 vs. 2 patients with depression). Young

people with depression miss fewer days of school and young people with depression are much more likely to exhibit aggression and antisocial acts (Carter *et al.*, 1995).

Personality

Four cross-sectional studies have investigated different personality characteristics in young people with CFS. In comparison to a control group of young people with juvenile idiopathic arthritis (Rangel *et al.*, 2003; Rangel *et al.*, 2000a), a CFS group had higher levels of personality difficulty and disorder. Using the Personality Assessment Schedule (Tyrer & Alexander, 1979) which is a parent-reported interview, the CFS group scored more highly for conscientiousness (Rangel *et al.*, 2003; Rangel *et al.*, 2000a), vulnerability (i.e. specifically disturbed when things go wrong; (Rangel *et al.*, 2003; Rangel *et al.*, 2000a)), worthlessness and lability (Rangel *et al.*, 2000a), sensitivity, eccentricity, anxiousness and rigidity (Rangel *et al.*, 2003). Self-report measures revealed that CFS patients had more problems with internalising symptoms (such as fearful or inhibited behaviour) than cancer patients (Pelcovitz *et al.*, 1995) and CFS patients were more likely to be withdrawn or have somatic complaints in comparison to healthy norms (van Middendorp *et al.*, 2001). The sample sizes of these studies are all quite small, between 30 and 58.

A more recent prospective study (Kato *et al.*, 2006); (see "studies in childhood informing adult diagnoses of CFS") investigated the link between personality measured in childhood and a diagnosis of CFS in adulthood.

Self-esteem

Unfavourable scores on self-esteem - especially in social competence – have been reported in CFS patients, in comparison with healthy (Garralda *et al.*, 1999; Kennedy *et al.*, 2010a) and normative controls (van Geelan *et al.*, 2010). When compared to a group with emotional disorders (Garralda & Rangel, 2005), the CFS group were comparable on self-esteem; the only exception was behavioural conduct in the CFS group ($p=0.009$). This sub-scale includes items such as "usually do what is expected of them" or "behave very well". Normal adjustment in terms of psycho-social self-esteem compared to normative controls (van Middendorp *et al.*, 2001) has been reported in one study of CFS. These were all cross-sectional studies. A recent meta-analysis of 621 studies investigating low self-esteem in people with chronic illness and healthy controls revealed that young people with chronic illnesses had lower self-esteem than healthy controls. Further, lowest self-esteem was observed in the young people with CFS and those with chronic headaches (Pinquart, 2012).

High Expectations

Differences in expectations and perceptions have been reported in young people with CFS compared to healthy young people in three different realms; fatigue levels (Garralda & Rangel, 2001) activity levels (Fry & Martin, 1996) and high expectations in relation to IQ (Godfrey *et al.*, 2009). Each of these studies were cross-sectional in design, taking into account both child and parent expectations.

Either young people with CFS and / or their parents significantly underestimated the young persons' current activity levels and had higher expectations of their post-CFS activity levels than was realistic for that age (Fry & Martin, 1996). The subjective rating

(as measured by visual analogue scales) of activity was significantly lower in the CFS group than the healthy control group, but the actual activity level measured over three days with an activity monitor was comparable across groups. Corresponding with these findings, in another study (Garralda & Rangel, 2001), young people with CFS had unrealistic views of normative fatigue levels as measured by an 11-point visual analogue scale (0 = no fatigue). Expected normative fatigue levels were significantly lower ($p = .001$) in the young people with CFS (median = 1.2) than in a healthy control group (median = 4). Another study found that parental expectations of IQ were significantly higher for young people with CFS than for healthy controls (Godfrey *et al.*, 2009). The patients' own self-estimates were not so high and overall, there was no significant difference between the groups on actual measured IQ.

Attributions

Several studies have investigated child or parental attributions about the cause of the CFS. Garralda & Rangel (2001) reported that 90% of young people with CFS and 72% of parents attributed the cause of their illness to biological factors in their cross-sectional study. Similarly Kennedy *et al.* (2010a) found 88% of young people reported their CFS had an infectious onset. In another study of 85 young people with CFS using a cross-sectional design, thirty-six possible causes of CFS were noted, with 33% saying the cause was a virus (Gray & Rutter, 2007). Smaller qualitative studies also found that physical causes were most widely (Richards *et al.*, 2006) or exclusively reported (Hareide *et al.*, 2011; Jelbert *et al.*, 2010). Rangel *et al.* (1999) described young people with CFS as wary of psychological explanations for symptoms. Hareide *et al.* (2011) reported that two-thirds of the nine adolescents interviewed rejected a psychological

cause. However there is evidence that a small minority of young people with CFS do make psychological attributions. Gray and Rutter (2007) found that 13% of their sample attributed the CFS to stress or worry and Richards *et al.* (2006) found that family and education-related stresses were reported as causes by some young people interviewed.

Illness perceptions and cognitions

Beliefs and perceptions may have important consequences for peoples' behaviour. Gray and Rutter (2007) found, using the Illness Perceptions Questionnaire (IPQ (Weinman *et al.*, 1996); IPQ-R (Moss-Morris *et al.*, 2002)) that illness representations formed characteristic patterns that were cross-sectionally associated with both physical functioning and quality of life (through self-reported daily functioning). Those young people with CFS who reported fewer symptoms and also those who reported their illness was caused by risk factors (hereditary, diet, poor medical care in the past, own behaviour, aging, smoking and alcohol) also remained more active, with a perception of better functioning. Contrary to what has generally been reported in studies of adults, the young people in this study perceived the symptoms and pattern of their illness to be more cyclical than chronic. Both more symptoms and a greater focus on symptoms were associated with poorer quality of life.

Van de Putte *et al.* (2005) explored the locus of health control in 32 young people with CFS and their parents in comparison with 167 healthy young people and their parents. Using the Multidimensional Health Locus of Control questionnaire (MHLC (Wallston *et al.*, 1978), this cross-sectional study found significantly less internal health control in young people with CFS than in healthy controls, as well as higher external loci of control in young people with CFS and their parents. Another cross-sectional study (Garralda & Rangel, 2004) compared impairment and illness attitudes of 28 young

people with CFS, 30 young people with juvenile idiopathic arthritis and 27 with emotional disorders. Using interviews, young people with CFS reported significantly more illness impairment, especially school attendance than those with juvenile idiopathic arthritis or emotional disorders. The young people with CFS reported generalised illness worry and particular styles of coping (such as emotion regulation and resignation) with illness and disability. Further, Brace *et al.* (2000) reported that young people with CFS (n = 10) scored significantly higher than the juvenile rheumatoid arthritis group (n = 14) on the measure of parental reinforcement of illness behaviour. Specific interest has focused on beliefs about rest and activity in patients with CFS (Richards *et al.*, 2005). In this cross-sectional study, a group of CFS patients (10-19 years) tended to prefer rest rather than exercise as a coping strategy in comparison to the group of young people with inflammatory bowel disease. A preference for rest over exercise was associated with a greater level of functional impairment and higher levels of reported fatigue.

Parental involvement

Maternal distress

It has been suggested that CFS in young people is influenced by functioning within the family. More specifically, Rangel *et al.* (2000b) suggested a link between maternal distress and poor outcome in young people with CFS. Five cross-sectional studies (Chalder *et al.*, 2003; Missen *et al.*, 2012; Rangel *et al.*, 2005; Rangel *et al.*, 2000b; van de Putte *et al.*, 2006) have investigated the association between maternal distress and fatigue.

In a community sample, distress in the mother was associated with parental report of CFS in the child (Chalder *et al.*, 2003). The mothers' psychological distress was assessed by the General Health Questionnaire (GHQ (Goldberg & Hillier, 1979; Goldberg & Williams, 1988)). This finding is supported by two small, cross-sectional studies (Rangel *et al.*, 2005; Rangel *et al.*, 2000b). In the Rangel *et al.* (2000b) study, more maternal psychiatric symptoms on the GHQ and more mothers with chronic health problems were reported in a poor outcome group of young people with CFS compared to the better outcome group (p=0.08). There was not a control group in this study. In 2005, the same authors reported greater current mental distress in the parents of the CFS group than a juvenile rheumatoid arthritis parent group as indicated by higher scores on the GHQ (Rangel *et al.*, 2005). A more recent cross-sectional study (Missen *et al.*, 2012), found that 72% (of 40) of mothers of young people with CFS scored above the cut-off on the GHQ compared with 20% of healthy control mothers.

Van de Putte *et al.* (2006) cross-sectionally found depression to be the main risk factor for the presence of CFS in the child, where distress in the mother corresponded with a 5.6 times higher chance for CFS in the child. We cannot know whether the maternal distress is a consequence of the CFS in the child or vice versa due to the nature of the study.

Parental care and overprotection

Parental care is characterised by emotional warmth and intimacy and overprotection characterised by intrusion and control, according to the Parental Bonding Instrument (PBI (Parker *et al.*, 1979)). These constructs have been studied cross-sectionally, with CFS patients being compared with healthy controls (Garralda *et al.*, 1999), ill controls

with juvenile rheumatoid arthritis (JRA (Rangel *et al.*, 2005)) and ill controls with Emotional Disorders (ED (Garralda & Rangel, 2005)). Garralda *et al.* (1999) found that young people with a history of CFS did not perceive different levels of parental care and overprotection compared to the healthy control group on the Parental Bonding Instrument. Subsequent studies revealed contradictory findings.

Based on scores of overprotection, self-sacrificing and pre-occupation with the child, families of young people with CFS compared to families of juvenile rheumatoid arthritis (Rangel *et al.*, 2005) or emotional disorders (Garralda & Rangel, 2005) were characterised by significantly greater emotional over-involvement and reports of greater family burden. This over-involvement has not necessarily been associated with greater accuracy of parental perceptions about the child's illness experience. In a study of 14 young people with CFS, Vervoort *et al.* (2007) found that mothers and fathers were less accurate for 'CFS thoughts and feelings' than for beliefs related to 'other life events'. The accuracy was determined by comparing the actual content of the child's interview with the parent's inferred content. There was not a control group in this study.

Immune and endocrine factors

It is unclear whether and to what extent there are alterations in the immune functioning of young people with CFS. Ter Wolbeek *et al.* (2007) conducted a study to investigate the immune function in young people with CFS through blood sampling. They had 3 groups: CFS, fatigued and non-fatigued participants. The non-fatigued and fatigued groups were selected from a broader fatigue study in secondary schools (ter Wolbeek *et al.*, 2007), whereby all girls were written to for this current study. The fatigued group did not meet criteria for CFS. Eleven CFS patients were recruited from a specialist CFS

unit. The eleven female CFS patients (mean age 15) showed similarities in self-reported complaints (including assessment of fatigue, anxiety and depression as well as school attendance) with the fatigued participants but not the non-fatigued participants. However, the CFS patients showed a distinct immune profile when compared to the severely fatigued and the non-fatigued participants, with increased levels of anti-inflammatory cytokines and reduced levels of pro-inflammatory cytokines. Cytokines help to regulate the immune system and these fatigued patients showed a 'skewing' of the cytokine balance towards an anti-inflammatory profile in comparison to the non-fatigued participants. Studies in adults have been published, but with contradictory findings (Cho *et al.*, 2006; Lyall *et al.*, 2003).

A cross-sectional study with 25 young people with CFS and 23 healthy controls (Kennedy *et al.*, 2010) was conducted to investigate biochemical and vascular aspects of CFS. They reported increased oxidative stress, with reduced levels of vitamins C and E as well as increased white blood cell death in the young people with CFS. This group reported similar findings in an adult population with CFS (Kennedy *et al.*, 2005). Recent studies (Kennedy *et al.*, 2005; Spence & Stewart, 2004) have shown that oxidative stress (OS) may be involved in the pathogenesis of CFS. Oxidative stress has been defined as a disturbance to the equilibrium status of pro-oxidant and antioxidant systems in favour of pro-oxidation. Oxidative stress can cause disruptions in normal mechanisms of cellular signalling.

Researchers have also started to investigate the Hypothalamic Pituitary Adrenal (HPA) axis function in young people. This is a major part of the neuro-endocrine system that controls reactions to stress. Hypocortisolism is described in adults with CFS (Cleare, 2003). A case-control study (Segal *et al.*, 2005) reported that young people with CFS

(N=23) had significantly lower mean cortisol levels than age matched controls (N=17) in response to a low dose synacthen test (LDST). Kavelaars *et al.* (2000) found no differences in baseline or corticotrophin releasing hormone (CRH) induced cortisol between 15 CFS patients and healthy controls, but baseline adrenaline levels were significantly higher in CFS patients. Wyller *et al.* (2010) found that serum cortisol concentrations in 67 young people (12-18 year olds) with CFS were no different to cortisol levels in 55 healthy controls. They measured the serum concentrations from blood samples between 8 and 9am in all participants.

The autonomic nervous system has been investigated in several ways in young people with CFS. A number of studies have used the Head-Up Tilt (HUT) (Benditt *et al.*, 1996) task to produce orthostatic stress, in order to investigate cardiovascular regulation. Using the tilt procedure, significantly fewer episodes of orthostatic intolerance (OI) in the control group than the CFS group have been reported (Galland *et al.*, 2008; Stewart *et al.*, 1999). Orthostatic intolerance is defined as the development of symptoms during upright standing relieved by recumbence or sitting back down again. It occurs because standing upright is a fundamental stressor. People who suffer from orthostatic intolerance lack the effective circulatory and neurologic mechanisms to compensate for the blood pressure changes.

Lower Heart Rate Variability (HRV) in the CFS group compared to controls ((Stewart *et al.*, 1998b); (Stewart, 2000)) both at rest and during tilt has consistently been reported using the HUT. Wyller *et al.* (2007c) also noted that the CFS group had a greater increase in the LF/HF ratio (low frequency / high frequency ratio) during tilt than the controls. LF/HF ratio is a measure of sympathovagal balance. Low frequency (LF) reflects a mixture of sympathetic and parasympathetic activity and high frequency (HF)

is a marker of parasympathetic activity (i.e. quicker changes in heart rate). More recent studies (Kennedy *et al.*, 2010; Sommerfeldt *et al.*, 2011) used the head up tilt task to investigate autonomic cardiovascular responses. They reported that during the task, the young people with CFS experienced increased heart rate, systolic blood pressure and LF/HF ratio compared to the healthy comparison group. Using a different orthostatic challenge test, a hand-grip task (Wyller *et al.*, 2011; Wyller *et al.*, 2008), researchers found significantly higher heart rate and lowest heart rate variability responses in the young people with CFS compared to healthy controls leading to enhanced sympathetic predominance of heart rate control. A recent study (Hurum *et al.*, 2011) compared ambulatory recordings of heart rate and blood pressure in 44 young people with CFS with healthy controls. The authors reported that both during the day and at night, heart rate was significantly higher in the CFS group, as well as higher blood pressure in the CFS group during the night. This adds support to the above evidence of sympathetic predominance of cardiovascular control in young people with CFS.

In contrast to the above studies, Katz *et al.* (2012) found no evidence that orthostatic intolerance was implicated in CFS. Using a cohort of young people with CFS (N=36) and recovered controls following infection mononucleosis (N=43), they tested orthostatic tolerance using a standing orthostatic tolerance test. There were 25% of young people with CFS and 21% of recovered controls with an abnormal standing orthostatic tolerance test result – not a significant difference between groups.

Investigating changes in cardiovascular control in response to the head up tilt over time, Sulheim *et al.* (2012) reported that compared to baseline, young people with CFS (N=47) had significantly lower heart rate, blood pressure, total peripheral resistance index (TPRI) and LF/HF (HR ratio) 3-17 months later. TPRI is associated with blood

pressure as it is the amount of resistance to blood flow present in the vascular system of the body. The patients also showed significantly less pronounced increases in heart rate, mean blood pressure, diastolic blood pressure and total peripheral resistance index during tilt compared to the first visit. However, there was not a significant correlation between improvements in responses to the head up tilt and changes in self-reported fatigue or functioning. Between baseline and time 2, all patients had been given symptom management advice and 27 reported having tried graded exercise therapy, cognitive behaviour therapy or drug treatment (propranolol or fludrocortisone).

Activity levels

Rangel *et al.* (2000b), asked CFS patients through interview and questionnaires about their ability to carry out activities at home and found significant differences between young people who had recovered and those who still met diagnostic criteria for CFS. The authors concluded that "a serious reduction in physical activity itself seems likely to have been a perpetuating factor for physical and mental malaise". However the direction of causality cannot be ascertained in this cross-sectional study as all patients had received treatment.

There is some evidence from pilot treatment studies that engaging in exercise may be beneficial for young people with CFS. An uncontrolled study found that young people with CFS generally reported a significant improvement from baseline scores when completing either resistance training or aerobic training (Gordon *et al.*, 2010). Likewise, Gordon & Lubitz (2009) reported that levels of fatigue improved by 13% after exercise training was introduced in a 4-week in-patient programme for young people with CFS.

Cognitive behavioural treatment trials which also focus on increasing activity will be described later.

Sleep

One prospective case-control study found significantly greater amounts of time spent sleeping in young people with CFS compared to matched (age and Tanner stage) non fatigued controls after EBV infection (Huang *et al.*, 2010; Katz *et al.*, 2009). When maintaining similar levels of exercise as the mononucleosis-recovered controls (6 months after diagnosis), young people with CFS reported significantly higher levels of fatigue and spent significantly more time sleeping during the day 6 and 12 months following infection.

Body mass index (BMI)

A recent study in the US (Petrov *et al.*, 2011) conducted a retrospective cohort study of 53 participants aged 9-18 years. Greater body mass index (as measured at diagnosis) was significantly associated with prolonged duration of CFS. The assessment of body mass index at diagnosis revealed an increased prevalence of overweight patients with the duration of CFS lasting for more than 24 months. Increased body mass index may be a consequence of restricted physical activity in young people with CFS.

Precipitating or triggering factors

Infection

Infectious Mononucleosis (IM), also known as Epstein-Barr-Virus (EBV) or glandular fever may be a risk factor for CFS in young people. In cross-sectional (Feder *et al.*, 1994; Kennedy *et al.*, 2010a; Krilov *et al.*, 1998; Patel *et al.*, 2003; Sankey *et al.*, 2006; Smith *et al.*, 1991) and retrospective-cohort (Petrov *et al.*, 2011) designs, several studies found that a high percentage of patients with CFS report that their fatigue began with an acute illness. Between 60% (Krilov *et al.*, 1998) and 93% (Sankey *et al.*, 2006) of the patients indicated that the fatigue had begun with an acute infective illness and there was evidence of past or present Epstein-Barr virus in some (5% – 36%) of the patients (Krilov *et al.*, 1998; Marshall *et al.*, 1991; Sankey *et al.*, 2006). A case-control study (Galland *et al.*, 2008) showed 10 out of 26 patients were confirmed positive for Epstein-Barr virus via antibody detection. Only 2 of the healthy control group (N=26) reported any subjective history of glandular fever-type illness. Petrov *et al.* (2011) identified Epstein-Barr virus in 66% of 53 CFS patients (aged 9-18 years), but there was no control group in this study. In a population based study, Nijhof *et al.* (2011) reported that in 22% of cases the illness started with an acute infection and in fact, in 52% of these young people, there was evidence of current or recent Epstein-Barr virus.

There is also prospective evidence of post-infectious CFS in young people. Katz *et al.* (2009) screened 301 young people (12-18 years) for non-recovery 6 months after infection mononucleosis, at which point 13% met the criteria for CFS. At 12 and 24 months, 7% and 4% respectively met the criteria for CFS. These rates are approximately 20 times higher than the 0.18% found in the general adolescent population (Jordan *et al.*, 2006).

Studies in childhood informing about adult diagnoses of CFS

Several studies have investigated childhood experiences in relation to a diagnosis of CFS in later life. A prospective study (Kato *et al.*, 2006) considered emotional instability and stress in CFS-like illness, where individuals reported at least 4 of the 8 symptoms set out by Fukuda *et al.* (1994). Higher emotional instability and self-reported stress in the pre-morbid period were associated with higher risk for CFS-like illness, 25 years later.

There have been three longitudinal studies investigating the relationships between activity levels in childhood and the onset of CFS in adults. In the first, lower levels of exercise in childhood were associated with a greater risk of CFS in later life. Identified by self-report at age 30, the reported age at onset of CFS ranged from 14 to 29 years (Viner & Hotopf, 2004). This study also found that high levels of exercise in childhood, as defined by "playing sport often in their spare time", had a significantly lower risk of CFS. Conversely, a second study, which defined high levels of exercise as "engaging in sporting activities weekly", in childhood through to adulthood (13 years to 43 years) found high levels of exercise were associated with an increased future risk of self-reported CFS in adulthood (Harvey *et al.*, 2008). This was a prospective study following participants in the first 53 years of their life, investigating predictors of a CFS diagnosis between the ages of 41 and 53. A third study did not replicate either of these studies finding no prospective association with either little exercise or lots of exercise in childhood and self-reported CFS in adulthood (Goodwin *et al.*, 2011).

Early adverse experiences such as childhood illness or trauma have been investigated in adults with CFS. In three retrospective population-based studies of adult CFS patients and non-fatigued control participants, the CFS patients reported significantly higher

levels of childhood trauma compared with the controls (Heim *et al.,* 2009; Heim *et al.,* 2006; Kempke *et al.,* 2013). These studies used the Fukuda diagnostic criteria (Fukuda *et al.,* 1994). The Heim *et al.* studies used a self-report Childhood Trauma Questionnaire (CTQ; (Bernstein & Fink, 1998)), with moderate to severe cut-off scores. The Heim *et al.* (2009) study reported above also showed that adults with CFS who reported childhood trauma had flattened cortisol awakening response profiles compared with well control participants. In this retrospective study, adults with CFS who did not report emotional maltreatment during childhood exhibited normal cortisol profiles. The authors suggest that childhood trauma might cause long-term impairment in terms of the ability to successfully adapt to stress, for example via disturbances to the HPA axis, thereby conveying a risk to developing CFS. Kempke *et al.* (2013) found that over half of the 90 adult CFS patients reported at least one form of childhood trauma on the Childhood Trauma Questionnaire. The most common was emotional trauma (46.7%). Total trauma and emotional abuse scores, and a higher number of trauma types were associated with higher levels of daily fatigue and pain over a 14-day period when controlling for demographic characteristics and depressed mood.

Fisher & Chalder (2003) also used a retrospective case-control design to compare early illness experience (up to the age of 16) between 30 adults with CFS, diagnosed at a tertiary referral clinic and 30 patients attending a fracture clinic. No differences were found between the two groups on any self-reported childhood illness category but they found increased levels of childhood maternal over-protectiveness in those with CFS compared with the ill controls.

A prospective study (Harvey *et al.,* 2008), reported those with CFS at age 53 years were no more likely to have experienced childhood illness than the healthy participants. In

another longitudinal study, Viner & Hotopf (2004) reported no association between maternal psychological distress in childhood/adolescence (measured by the Rutter Malaise Inventory (Rutter *et al.*, 1970)) and risk of CFS in adulthood as reported by questionnaire.

Discussion of the literature

Main findings

Ethnicity is not widely reported in studies investigating CFS in young people. Jones *et al.* (2004) in a study in the US reported that 72.2% of the population was white. However, when ethnicity was measured in adult studies, a small number of community based studies (Alisky *et al.*, 1991; Steele *et al.*, 1998) reported higher rates of fatigue among certain ethnic groups. For example, Jason *et al.* (1999b) reported that African American and Latino populations had significantly higher fatigue scores than populations of Caucasian people.

Most studies in the UK report a female excess of two thirds to a third (Dowsett & Colby, 1997; Farmer *et al.*, 2004; Patel *et al.*, 2003) as do the US studies (Bell *et al.*, 1991; Dobbins *et al.*, 1997) and an Australian study (Lloyd *et al.*, 1990). Crawley & Sterne (2009) reported that 69.2% of their sample was female which is consistent with the specialist cohorts (Bell *et al.*, 2001; Feder *et al.*, 1994; Krilov *et al.*, 1998; Rangel *et al.*, 2000b). Of the studies reviewed, the strongest evidence regarding the aetiology of CFS in young people is that the Epstein-Barr virus (EBV) is associated with an increased risk of CFS. A prospective study found that CFS developing after infection was 20 times more likely than in the general population (Katz *et al.*, 2009). However,

most individuals who experience EBV do not go on to develop CFS, so an understanding of other contributory factors is required.

This review identified strong evidence of increased rates of psychiatric co-morbidity in young people with CFS compared to healthy or ill control groups. Depressive disorders and anxiety disorders are the most commonly reported co-morbid problems. From such cross-sectional studies it is not possible to ascertain the direction of causality. In adults there is evidence from prospective studies that psychiatric disorders increase the risk of subsequent CFS (Wessely *et al.*, 1996). A prospective study of young people found that anxiety, depression and conduct disorders at time 1 were associated with increased fatigue and chronic fatigue 4-6 months later (Rimes *et al.*, 2007). It is suggested that this may be both a predisposing and perpetuating factor for CFS in young people. However more research is needed into this issue. ter Wolbeek *et al.* (2011) reported that vulnerability to develop fatigue and associated symptoms in young adulthood can to a certain extent be identified already, years before the manifestation of complaints. They found that in young people who experienced a notable increase in fatigue, fatigue development was preceded by emotional problems and CFS-related complaints during adolescence. The nature of the association is unknown. It is possible that genes, early life experiences and learned psychological responses act individually or together (e.g. via differences in HPA-axis responding) as risk factors for both psychiatric disorders and CFS.

There are some measurement issues which warrant discussion. Some studies (n = 13) used self-report questionnaires to identify symptoms of anxiety or depression (Fry & Martin, 1996; van Middendorp *et al.*, 2001). These self-report scales measured psychological distress and symptoms of anxiety or depression. Fewer studies (n = 6) used semi-structured interviews to make clinical diagnoses of anxiety and / or

depressive disorders (Garralda & Rangel, 2005; Garralda *et al.*, 1999; Heim *et al.*, 2009; Rangel *et al.*, 2003; Rangel *et al.*, 2000b; Smith *et al.*, 1991). Both self-report measures and clinical interviews reported higher rates of anxiety and depression symptoms in the CFS group than the illness controls. However, caution must be taken when interpreting results of studies using self-rating scales as they are not necessarily evidence of a diagnosis of clinical anxiety / depression. Interviews have some advantage over self-report measures as they capture all information needed for a diagnosis (Cohen *et al.*, 1993).

It is clearly important to have developmentally sensitive assessment tools. This can prove challenging in this age group (Beesdo *et al.*, 2009) and one should be aware of developmental issues as a possible limitation to both semi-structured interviews as well as self-report scales. With adolescents however, this is less of a problem and clinicians can more confidently make diagnostic decisions based on the self- report by the young person rather than relying on parental report (Schniering *et al.*, 2000).

The emergence of certain psychopathologies during adolescence could be related to typical adolescent maturation changes which occur in concert with psychosocial factors (e.g. school or social stresses). This time period appears to be the central period of risk for the development of mild symptoms of anxiety through to full anxiety disorders (Kessler *et al.*, 2005), depression (Cyranowski *et al.*, 2000) and chronic fatigue and CFS (Chalder *et al.*, 2003; Rimes *et al.*, 2007). Given that anxiety disorders and depression have been found to be associated with chronic fatigue and they occur at a similar stage of development it seems likely that these disorders have some common risk factors. These may include stress (Cohen *et al.*, 1987), parenting style and certain vulnerable personality characteristics.

Some evidence was found for certain personality traits, including excessive conscientiousness, rigidity, fearful behaviour and sensitivity being reported more frequently in young people with CFS (Pelcovitz *et al.*, 1995; Rangel *et al.*, 2000a; van Middendorp *et al.*, 2001). As personality traits are generally assumed to be persistent individual characteristics, it is suggested that these may be predisposing factors. Indeed it is not difficult to speculate that being excessively conscientious or rigid may make it more likely for the individual to become stressed and hence more fatigued in the context of extra challenges such as physical illness or life events. However, due to the cross-sectional nature of these studies, the possibility of personality change occurring as a result of CFS cannot be ruled out. However, there is a lot of research to support the notion that personality shows great continuity from the age of 3 throughout the adolescent years and into adulthood (Caspi, 1998). For example, if a young child was shy and inhibited, they are more likely to be anxious and inhibited when they reach adolescence (Kagan *et al.*, 1994). Recent research using different methodologies suggests that personality can be reliably assessed in adolescence (Westen *et al.*, 2003).

There is consistent, cross-sectional evidence of high expectations in young people with CFS in comparison to control groups. Inaccurate expectations and unrealistic perceptions were reported with regards to fatigue, activity and IQ levels, in young people with CFS and their parents. High standards appear to be problematic in a general sense across aspects of life (Garralda & Rangel, 2001; Godfrey *et al.*, 2009). Evidence for an association between maternal distress and CFS in young people has been shown in cross-sectional research. Again the causal direction cannot be ascertained and clearly it is very stressful for parents to have a child with a chronic health problem. Children with psychosocial problems are more likely to have mothers who are depressed (Downey & Coyne, 1990), and mothers with depression are more likely to

report psychosocial problems in their children (Boyle & Pickles, 1997a; Boyle & Pickles, 1997b). Rimes *et al.* (2007) prospectively found that maternal distress at time 1 was associated with the persistence of fatigue as well as new onset Chronic Fatigue at time 2 (4 to 6 months later). Although not CFS specifically, it suggests maternal distress may be contributing to CFS-like symptoms.

A family history of CFS seems to be associated with an increased risk of CFS in young people (Bell *et al.*, 1991), but the nature of genetic vulnerability and how this might interact with environmental factors is not known. Sommerfeldt *et al.* (2011) reported differences in adrenergic receptors of young people with CFS which are associated with enzyme activity, which may affect sympathetic nervous activity.

Research into the pathophysiology of CFS is in its infancy. Subtle differences in cortisol response profiles and HPA axis function in young people with CFS patients in comparison to healthy controls has been reported in one cross-sectional study (Segal *et al.*, 2005). However, HPA disturbance has been well-documented in adults with this condition (Cleare, 2003). In adults with CFS a study found that only patients with a history of childhood trauma showed a reduced cortisol response but this association has not been investigated in young people (Heim *et al.*, 2009). There is some cross-sectional evidence of differences in autonomic arousal in young people with CFS, with young people with CFS having lower HRV than controls during a HUT task and significantly higher HR than healthy controls (Wyller *et al.*, 2008; Wyller *et al.*, 2007c). There is preliminary evidence that these differences in cardiovascular response normalise over time but there was no indication that these improvements correlated with self-reported improvements in symptoms or functioning (Sulheim *et al.*, 2012). From the cross-sectional evidence, it is unknown whether these physiological differences contribute to the initial development of the condition but they may well be contributing to the on-

going symptom experience. There are many possible causes of these physiological differences including stress or changes in activity or other health behaviours associated with the condition. The hypothesis that differences in physiological responding in conditions of stress is a pre-existing risk factor for CFS needs further investigation, especially in prospective studies.

Cross-sectional research has consistently reported that young people with CFS (and their families) attribute the cause of their CFS to a physical / biological cause, often rejecting a psychological explanation. This is not necessarily surprising given that in many cases the fatigue began in the context of a virus. However, families may be overlooking other factors that made the young person vulnerable for fatigue becoming a more chronic problem. It has been suggested in adult models of CFS that the tendency to make somatic attributions is due to beliefs about negative emotions being unacceptable and a sign of weakness (Surarwy *et al.*, 1995). In adults there is evidence that such beliefs are indeed reported to a greater extent in people with CFS than healthy individuals (Rimes & Chalder, 2010) but this has not been investigated in young people or their parents.

Cross-sectional studies investigating levels of over-protection (control and higher levels of parental care) in young people with CFS have thus far produced mixed findings. It could be argued that over-protection is a natural response to a chronically ill child, or may be in response to characteristics already shown in the child. However, it is also possible that parental responses may be acting inadvertently to perpetuate the fatigue and / or disability in young people with CFS. For example, in their understandable efforts to aid recovery, parents may be inadvertently encouraging too much rest which could cause de-conditioning and make young people cautious or fearful about engaging in activity. Indeed a retrospective study reported that increased levels of maternal

overprotection in childhood were found in participants with a diagnosis of CFS in adulthood. This was in comparison to a fracture clinic group of patients – suggesting that overprotection is not purely a response to an ill child. It may be that communication from an adult to a child about being cautious in response to a range of situations may be relevant to the formation of fearful belief systems in the child. In some this may contribute to the development of CFS. It is also possible that maternal over-protection is illness-focused and that cognitions develop which are centred around fear of increasing symptoms which then leads to the avoidance of activity, which has been found to be an important maintaining factor in adult CFS (Vercoulen *et al.*, 1994).

Little is known about the role of physical activity in the development of CFS in a child and adolescent population. The only studies investigating this area have been prospective studies which have found contradictory results regarding childhood activity levels acting as a risk factor for adult-onset CFS later in life. Both too little (Viner & Hotopf, 2004) and too much (Harvey *et al.*, 2008) exercise have been identified as risk factors. A small, cross-sectional study (Rangel *et al.*, 2000b) noted that a reduction in activity may perpetuate the disorder. Objective measurements of physical activity would improve our understanding, as self-reports of activity levels are not necessarily reliable. It is possible that prolonged inactivity leads to physical de-conditioning such that symptoms emerge at progressively lower levels of physical activity. On the other hand, many patients report being very active before they developed CFS symptoms (Harvey *et al.*, 2008).

Key Limitations of the existing literature

The key limitation is that most of the studies which were experimental or questionnaire-based were cross-sectional in design with only one time point. This makes specifying the direction of causality impossible. Future prospective studies should include longer periods of follow up. Furthermore we cannot yet answer questions regarding the relative contributions of these factors to the development and perpetuation of CFS in young people.

Some studies did not use a control group which means it is not clear whether the results are specific to CFS or may be true for other chronic illnesses or indeed the general population. Additionally, there is reliance in many of these studies on self-report measures. This subjectivity means limited conclusions can be drawn. Also, different measures across studies can make it difficult to compare results. Many of the studies used patients drawn from specialist settings. However, it may be that those seen in the specialist clinic are representative of a clinical population. Many of the studies used small samples, which may mean the findings cannot be generalised to larger populations.

A final limitation is that not all studies have used the same diagnostic criteria to identify participants for study inclusion. However, although there should be some caution in comparisons across studies the diagnostic criteria are not very different from one another and most studies used the Fukuda criteria (Fukuda *et al.*, 1994).

Limitations of the review

A number of limitations of this review must be considered. Firstly, all of the studies discussed here are published studies. It was beyond the scope of the review to locate any unpublished research or to search the 'grey literature'. With this in mind, there may be a potential for publication bias. The search strategy used here is not exhaustive, so it is possible a study has not been identified, although unlikely given all reference lists were searched as well.

Due to the heterogeneity of the studies, an overall statistical synthesis of findings was not possible. However the review highlights areas for useful future study and the findings have helped to contribute to the development of a model of CFS in children and adolescents as suggested below.

Due to the emphasis the studies have placed upon chronic fatigue as the key symptom of CFS, there has been less emphasis here regarding other symptoms of CFS that may contribute to this associated disability experienced in CFS. For instance, in addition to the chronic fatigue are self-reported post-exertional malaise (Jordan *et al.*, 2000) and also neurocognitive dysfunction (Rowe & Rowe, 2002).

A hypothesised model of CFS in children and adolescents

A model incorporating the above-reviewed research findings whilst drawing on existing adult and child and adolescent models of CFS (Chalder *et al.*, 2002; Surarwy *et al.*, 1995; Wessely *et al.*, 1989) will now be described (also see Figure 1.1, page 68). Since the research presented in this review has primarily focused on vulnerability to

developing CFS in young people, this is the main focus of the following model but perpetuating factors are also included.

Vulnerability factors

A stress-diathesis model of chronic fatigue syndrome in young people is proposed. It is suggested that young people who go on to develop CFS are likely to have had a pre-existing vulnerability to stress which interacts with precipitating factors in the aetiology of this condition. There is likely to be variation in the form of this stress vulnerability. For example, this may take the form of personality characteristics, differences in physiological dysregulation responses, vulnerability to psychological distress, or beliefs about symptoms and illness. Physiological dysregulation is a condition by which the Autonomic Nervous System (ANS) malfunctions. Genetic factors are likely to have contributed to this stress vulnerability, although the exact nature of this contribution is unclear. Parental factors such as parental distress or overprotection may also contribute to stress vulnerability in their child, as will environmental factors such as abuse or other adverse experiences.

Personality factors such as high self-expectations or conscientiousness are likely to be associated with less flexibility in changing behaviour in the context of stress or illness (Surarwy *et al.*, 1995). This can mean that the young person keeps on trying to maintain high standards despite illness or other life demands, resulting in greater fatigue and stress. Stress vulnerability in terms of differences in autonomic arousal could mean that the young person experiences more physical symptoms than other individuals when under challenging circumstances. If the young person or their parents makes physical illness attributions for these symptoms, this may result in inadvertent unhelpful responses such as prolonged rest or school absence or reduction in everyday activities

rather than directly addressing the source of stress. It is suggested that for some young people, the pre-existing stress vulnerability has already resulted in clinically severe levels of distress, usually in the forms of depression or anxiety, which in turn put them at increased risk of developing CFS.

Precipitating factors and initial responses

A trigger for the development of CFS is often reported retrospectively to be an infection, other illness or stress. The only prospective evidence is for the role of the Epstein-Barr virus as an infective trigger (Katz *et al.*, 2009). However, most young people who experience such a virus do not go on to develop CFS so further factors must also be involved. Cross-sectional evidence summarised in this review is consistent with the suggestion that at least some patients with CFS may be vulnerable to stress and / or more sensitive to stress than healthy young people. Following a stress trigger such as a challenging life event, the young person will have experienced a stress response associated with a number of physical and mental symptoms, including fatigue, concentration problems and sleep disturbance. However, the individual may fail to recognise the cause of the symptoms and / or attribute the cause of the symptom to something physical. Several studies have reported physical attributions for illness in young people with CFS and their parents (Kennedy *et al.*, 2010a). It is not difficult to understand why a physical illness attribution may be made if the challenging life event, such as changing schools or exams, are things that other children are able to experience without such severe or prolonged physical symptoms, because they are less vulnerable to the effects of stress than the young person who goes on to develop CFS. Similarly, if

the fatigue was initially triggered by a virus, it makes sense that the family would view prolonged fatigue as a continued result of this causal factor, rather than taking into account that factors contributing to *persistent* fatigue may be different to those triggering fatigue initially.

Perpetuating factors

If there is an on-going stressful situation, the direct impact on fatigue levels will continue. However, once fatigue has developed, it is proposed that additional factors act to perpetuate the fatigue which may be different to those that initially triggered it. For example, the above-described factors associated with stress vulnerability in the young person may result in more negative and fearful beliefs about the symptoms themselves, such as meaning that they are seriously ill or that a small increase in fatigue could herald a major relapse. Such beliefs have been reported in adults with CFS but need investigation in young people. In an understandable response to such beliefs, the young person may use coping responses that can help control fatigue in the short-term but in the long-term will inadvertently add to symptom severity and impairment in daily living activities (Chalder *et al.*, 2002).

One such proposed maintaining factor is excessive rest, which can result in reductions in physical conditioning and difficulties tolerating normal activities. There is evidence from a cross-sectional study that young people with CFS tend to favour rest over exercise as a coping strategy (Richards *et al.*, 2005) but prospective evidence is still needed.

As the young person continues to experience fatigue and disability, they may reduce their daily activities further in an attempt to control the symptoms, including missing school or social activities. This puts them at risk of becoming more isolated from their peers and increasingly behind with their school work. This can contribute to the development of further distress, sometimes anxiety or depression, which in turn causes more fatigue and other physical symptoms. The young person may also increasingly focus on their symptoms in an attempt to try to understand or gain control over the fatigue. However, a greater focus on symptoms has been found to be associated with poorer quality of life in a cross-sectional study (Gray & Rutter, 2007).

The family may also respond in ways that inadvertently act to maintain fatigue. Parental distress may result in higher levels of on-going stress for the child, or parental responses such as over-protection may have the unintended effect of impeding the child in returning to normal daily activities. Advice from others outside of the family may also be inadvertently unhelpful, such as teachers or health professionals recommending rest or avoidant responses. These areas need further research.

Clinical implications of the review

The findings from this review have highlighted the complex nature of this condition. The exact aetiology of CFS in young people remains unclear, but existing evidence suggests that there are a number of variables involved in the development of symptoms and disability. It seems highly likely that both the symptoms of fatigue and the associated disability are a result of a complex interplay of cognitions, behaviour, physiology, emotional and social factors which have evolved over time. Each of these factors needs to be considered during treatment. As familial factors may be important in

the development and perpetuation of CFS it is suggested that the family should be involved in both the assessment and treatment. Both over-protection and maternal distress should be considered here. Given the overlap with psychiatric disorders management plans should address such problems. Treatment should be tailored to specific personality types, and should address certain individual characteristics such as high expectations and / or low self-esteem. Fisher and Crawley (2012) suggest that those with high levels of anxiety require individualised treatments tailored to their different types of anxiety as part of their treatment. The nature of the reported biological differences remains unknown, but it may be useful to monitor the subtle cortisol differences and lower HRV in young people with CFS during treatment to see how they change over time and whether the changes correlate with change in behaviour. There is preliminary evidence to suggest that cortisol levels normalise after CBT in adults (Roberts *et al.*, 2008) and in young people (Rimes *et al.*, unpublished-a). Treatment should also be tailored to take account of, stress and trauma where indicated.

Cognitive behaviour therapy attempts to address a range of factors that may be contributing to the condition including unhelpful beliefs and behaviours, and often this involves parents as well as the young person. Three randomised controlled trials provide evidence for treatment of CFS in young people. Stulemeijer *et al.* (*2005*) found that patients given a course of Cognitive Behavioural Therapy (CBT) over a 5 month period reported a significantly greater decrease in fatigue severity, functional impairment and their attendance at school improved significantly, as compared to a waiting-list control group. These findings were supported by Chalder *et al.* (2010) who found that initially after a course of family-focused CBT, school attendance and fatigue improved more in the CFS group than in the group of young people receiving psycho-education. However, this increase slowed and the psycho-education was as effective as the CBT group by 6

month follow-up. Both studies showed that improvements after CBT are maintained 5 months after treatment (Chalder *et al.*, 2010; Stulemeijer *et al., 2005*) and still 2 years after discharge from treatment (Lloyd *et al.*, 2012). Recently, a randomised controlled trial, found that an internet-based CBT treatment was significantly more effective than usual care across outcome measures: fatigue, school attendance, and physical functioning (Nijhof *et al.*, 2012).

A non-randomised cohort study investigating the role of telephone guided self-help for 63 young people with CFS reported a significant decrease in fatigue and a significant increase in school attendance between pre-treatment and 6 month follow-up, using principles of cognitive behavioural therapy (Lloyd *et al.*, 2012b). Early evidence from a pilot study suggests that a gradual increase in exercise may be associated with a decrease in levels of fatigue (Gordon *et al.*, 2010).

Where next?

All findings reported in the review would benefit from further evaluation. Well-designed studies addressing the methodological weaknesses raised above will enhance our understanding of the various factors. Large, prospective studies are needed. Experimental designs could help us better understand the cognitive, behavioural and emotional coping behaviours in young people with CFS. Beliefs about illness could be investigated experimentally. For example, as exercise gradually increases, beliefs concerning the link between increased activity and a worsening of physical symptoms could be evaluated. Research into the autonomic nervous system shows promising preliminary results and this could be a focus for future research, for example using experimental stress-induction paradigms.

This thesis will build upon the literature presented here and examine some of the aspects of the model presented (Figure 1.1, page 68). There has been very little research carried out and no previous studies have attempted to study a number of aspects of the model simultaneously.

This thesis will investigate some of the hypothesised risk factors for CFS (e.g. high self-expectations / perfectionism and negative beliefs about expressing emotions). It will also investigate, for the first time, factors that may act to maintain the fatigue such as increased physiological dysregulation in response to stress, misattribution of symptoms, symptom focusing, sleep disturbance and fear leading to avoidance of activity. This will be conducted through the use of both prospective questionnaire design as well as experimental studies, comparing young people with CFS with age-matched young people with asthma, and healthy controls.

Rationale, aims and hypotheses

This thesis reports questionnaire and experimental studies using cross-sectional and prospective designs to investigate the role of hypothesised factors in the development and perpetuation of CFS in adolescents. The main aim is to investigate the factors associated with predisposing, precipitating and perpetuating fatigue and disability in CFS in adolescents.

The first stage of the research is a cross-sectional questionnaire study investigating clinical characteristics of adolescents with CFS (chapter 3), and their mothers (chapter 4). A series of experimental tasks test various factors hypothesised to influence the fatigue, specifically symptom focusing, stress, (mis)attribution of symptoms, attention

and physical functioning. Exploratory analyses also involve the physiological aspects to the hypothesised model; heart rate, heart rate variability and skin conductance response (chapter 6) and cortisol levels (chapter 7). It is predicted that some of these factors act to maintain the fatigue and disability and these are investigated in the prospective study, where participants are followed up at stage 2, 8 weeks later (chapter 8).

The novel investigation into these factors is designed to support the development and refinement of an evidence based psycho-physiological model of CFS in adolescents. It is envisaged that by investigating contributory factors, the already effective interventions will be improved and tailored to meet specific needs of adolescents with CFS. The key objective is to investigate adolescents with CFS and compare them with adolescents with asthma and healthy control adolescents on various psychological and physiological variables. The main hypotheses and subsidiary hypotheses are presented below.

Main hypotheses

Questionnaire measures

The CFS group will exhibit significantly higher scores on subscales measuring negative beliefs about engaging in activity, catastrophising, damage beliefs (believing symptoms are a sign of damage), embarrassment avoidance, symptom focusing, all or nothing behaviour and avoidance behaviour than the asthma group. The CFS group will have significantly higher scores on perfectionism, neuroticism, and social desirability scales than the other 2 groups, as well as lower scores of extraversion as measured by the Eysenck personality questionnaire (EPQ). The CFS group will have significantly more

negative beliefs about the acceptability of experiencing or expressing negative emotions than the other 2 groups. The CFS group will have higher rates of psychiatric disorder than population norms. The CFS group will have significantly higher scores of depression and significantly higher scores of anxiety than either of the other 2 groups.

Maternal factors

Specific hypotheses are outlined in chapter 4, but include the measurement of maternal clinical characteristics. It is hypothesised that mothers in the CFS group will exhibit lower mood (symptoms of depression), higher levels of maternal neuroticism and anxiety, and more self-sacrificing behaviours compared to mothers of the two control groups.

The task session

1) Does symptom focusing increase symptoms of fatigue?

CFS adolescents randomly allocated to an experimental task inducing symptom-focusing will report greater levels of fatigue and other symptoms randomly allocated to a distraction task.

The control groups' level of fatigue and other symptoms will not be significantly affected by the condition to which they are randomised.

2) Pre-performance expectations and anxiety

It is hypothesised that adolescents with CFS will be more anxious, have lower expectations of their performance and greater expected difficulty, before the attention,

social performance and exercise tasks than the other two groups. It is predicted that these group differences will be particularly pronounced for the exercise task.

Preliminary analyses will be undertaken to investigate the relationship between pre-task expectations and objective task performance (time taken and / or accuracy or performance).

3) Post-performance self-evaluation

Due to hypothesised negative perfectionism in the adolescents with CFS, it is predicted that the discrepancy between their self-evaluation of performance and objective ratings will be larger in this group than the other two groups; their self-ratings will be more negative relative to objective ratings.

Actual performance on the different tasks (attention, social performance and exercise) will be reported, but the key hypotheses are the discrepancies identified in the above hypothesis.

4) Attributions of symptoms of stress

The CFS group will be more likely to attribute symptoms of physiological dysregulation (stress) caused by the social performance task to their illness than the asthma group and will be less likely to attribute the symptoms to stress.

5) Parental expectations

It is hypothesised that parental expectations will be lower in the CFS group because they view their child as particularly disabled by the CFS.

Physiological parameters

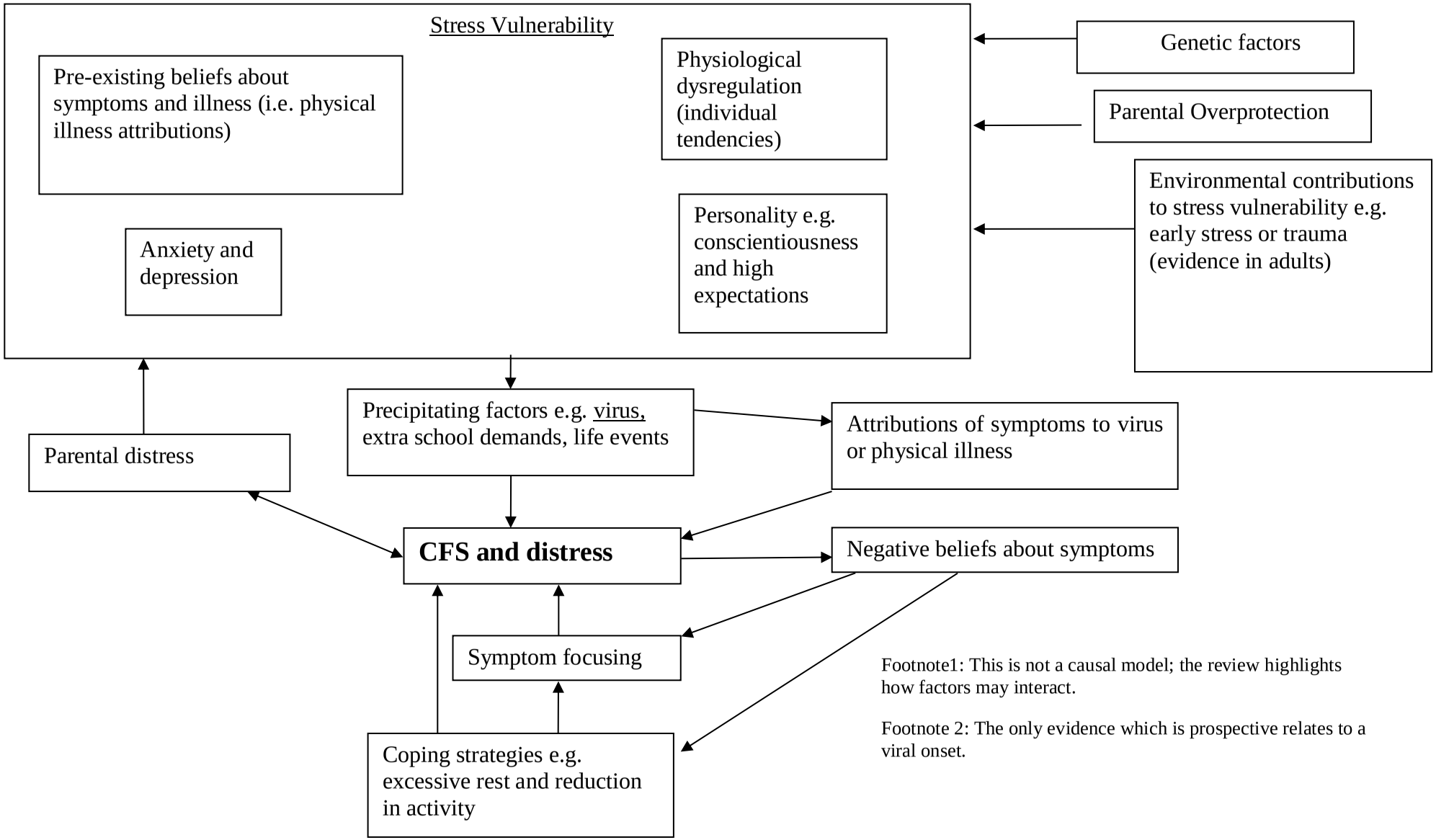
Heart rate will be significantly higher in the CFS group than the other two groups during the social performance task and in anticipation of the exercise task. There will be significantly greater increases in skin conductance response (SCR) in CFS participants compared to the other two groups associated with anticipation and experience of the stressful tasks. LF/HF ratio, the frequency domain of HRV will be higher in the CFS group than in the other two groups, but time-dependent heart rate variability (RMSSD) will be significantly lower in the CFS group than the other two groups on the two tasks, both at baseline and during the task. This is in line with the previous literature.

Under the stress of being asked to give a brief presentation, adolescents with CFS will show a blunted cortisol response and females in particular will show this pattern of disturbed cortisol responses compared to the other 2 groups with the adolescents with CFS having lower cortisol output.

Prospective study

It is hypothesised that symptom focusing, fearful beliefs about engaging in activity, avoidance of activity, perfectionism, unhelpful beliefs about emotions, all or nothing behaviours and maternal distress at time 1 will be associated with greater fatigue, physical functioning and school and social adjustment at time 2 (8 weeks later), according to the cognitive behavioural approach.

Figure 1.1: A hypothesised model of Chronic Fatigue Syndrome in children and adolescents based on research evidence



Chapter 2: Overall methodology

Synopsis

This chapter gives an overview of the methods used to test the psycho-physiological model of CFS in adolescents outlined in chapter 1. A cross-sectional and prospective case-control design was used to assess a sample of adolescents with CFS, adolescents with asthma, and a healthy control sample. The design, setting, sample selection, potential contributory factors investigated and follow-up methods are all described. Later chapters describe in greater detail the specific methods used within each part of the study. A summary of the pathway through the studies is presented.

Study design

A prospective case-control design with an 8-week follow-up stage was selected. This was a cross-sectional case-control study (time 1) with a prospective component (time 2). A prospective study assesses outcomes (such as fatigue) and relates this to other factors (hypothesised risk factors) measured at time 1. The sample is recruited to study the association between a factor at time 1 and an outcome at time 2.

This study included 3 participant groups; adolescents with CFS, adolescents with asthma, and healthy controls. The advantage of this design is two-fold. Firstly, a prospective design allows one to investigate directionality between associated factors. Understanding factors that predispose an individual to developing the condition and processes by which the condition is maintained should allow treatment to be improved. A cross-sectional design alone would not allow for investigation of the temporal direction of the association between factors, a limitation of most studies investigating adolescent CFS to date.

Having an illness control group as well as a healthy control group adds strength to this thesis. It allows one to investigate whether a difference between the groups is due to the experience of chronic illness in general or the specific illness one is investigating, in this case CFS.

The CFS group were consecutive patients attending two CFS services in London, for assessment of CFS. The asthma and healthy control groups were an opportunity sample. They replied to a letter about the study (as described further in the participants section on page 73).

The 8 week follow-up after initial assessment was chosen as a naturalistic period in which the CFS patients had not started treatment for their illness. Eight weeks marked long enough duration for symptoms and functioning to potentially have changed. The eight week duration was the typical length of time that patients would be on a waiting list for treatment so did not present ethical concerns in terms of delaying access to treatment. They could continue treatment as normal.

Ethical considerations

Ethical approval was sought and granted by the following bodies, the Local Research Ethics Committee (LREC; ref. 08/H0807/107), Institute of Psychiatry (September 2009, R&D), Guys & St. Thomas' Hospitals (March 2011) and Great Ormond Street Hospital (October 2010). Several amendments were submitted and approved during the study and are listed in appendix 1 (page 383).

It was possible that travelling to the clinic and the general effort involved in participation in the study could cause increased fatigue and other symptoms. There was no reason to expect this to result in anything more than a transient increase in symptoms but this issue was monitored throughout the study. No serious adverse consequences were reported.

In terms of data confidentiality, the requirements of the Data Protection Act (1998) were complied with. Participants were informed in the information sheet that only researchers in the CFS service would have access to their personal data. Participants' personal data was not saved on the database (e.g. name and address). Each participant was given a unique study identifier when they entered the study. Password protection for the

databases was used at all times to ensure security. All paper copies of data were locked in filing cabinets in the CFS service (again containing unique study identifiers not personal details).

Inclusion and exclusion criteria

CFS inclusion and exclusion criteria

The inclusion criteria were: 1) aged between 11-18 years; and 2) having a diagnosis of CFS using the CFS diagnostic criteria outlined by the Centres for Disease Control (CDC) (Fukuda *et al.*, 1994) (see appendix 2; page 384). All adolescents were assessed in one of the two services described below.

Exclusion criteria were: 1) any physical or psychological conditions that are known to cause fatigue symptoms and meant that the person did not meet diagnostic criteria for CFS, such as psychosis or an eating disorder (Fukuda *et al.*, 1994), any significant visual or auditory difficulty that would impact on their ability to take part in the study; 3) poor use of the English language; and 4) any risk such as self-harm which necessitated immediate treatment and care. All participants had been assessed by a paediatrician prior to being seen in the CFS clinic.

Asthma inclusion and exclusion criteria

All adolescents with asthma who had a medical diagnosis and used medication (e.g. inhalers) to manage their asthma were eligible. They were asked to rate the severity of their asthma on a mild-moderate-severe scale and record medication taken. Those not

needing medication for their asthma symptoms (n=8) were deemed ineligible for the study.

Healthy control inclusion and exclusion criteria

Individuals who were unable to read English were not asked to participate in the study. Individuals who had suffered with CFS or asthma in the past were excluded from the healthy control group.

Participant recruitment

Participants were recruited between August 2010 and December 2012.

Chronic fatigue syndrome

Patients with CFS were recruited from two specialist units for adolescents with CFS: King's College London / South London and Maudsley NHS Trust Chronic Fatigue Syndrome Research and Treatment Unit (n=74), and the Great Ormond Street Hospital Chronic Fatigue Syndrome Service (n=11).

Patients and their parents were given information sheets (appendix 3, page 387) at the initial CFS diagnostic assessment carried out at the services and the study was explained by the assessing clinician. A consent form was attached for the participants and accompanying parent to complete. Most participants returned their reply slips to the assessing clinician or to an administrator of the team (n=77). Others replied by post

(n=5). The initial non-responders were followed up by telephone after the assessment (n=22), having given verbal consent. Three of these agreed to take part.

A total of 25 patients declined to take part in the study. Thirteen felt the travel distance was too difficult and 12 were too ill to come to the CFS service for the study. Twenty-three patients completed the questionnaires but not the experimental tasks (completed during a one-off visit to the clinic on a separate occasion).

Five patients were assessed but were not suitable for the study. Table 2.1 highlights the reasons for exclusion. These patients were given the information sheet by the assessing clinician and they agreed to be part of the study if deemed suitable. Subsequently however, the researcher (author) found they did not meet the research criteria and called the families to explain.

Table 2.1: Reasons for exclusion from the study (CFS participants)

Reason for exclusion	**Number of participants**
Not CFS	2
Too young / old	3

Asthma

Thirty-one adolescents with asthma were recruited from GP practices in the Greater London area. A total of 246 general practitioner (GP) surgeries were initially contacted by a letter to the surgery. This included the asthma information sheet (see appendix 4, page 390). The letters were followed up with a phone-call, email or fax. This was repeated until the asthma nurse or practice manager had been spoken to. Following this, if the surgery agreed to be involved, a letter was sent to each adolescent with asthma at

the surgery, along with the contact form (see appendix 5, page 393) and a pre-paid envelope. If the adolescent and their family were interested in taking part in the study, they returned the form to the author. Appointments were then made to suit the adolescent and their families, in agreement with the GP surgery and depending on room availability. The majority (n=25) were seen at the GP surgery but some were seen at the CFS service at the Maudsley Hospital (n=6).

Of the 246 surgeries contacted, 7 agreed to participate in the study. This resulted in 413 letters being sent to possible participants. Thirty nine participants (and families) responded to the letter. Eight were deemed ineligible (no medications) and subsequently 31 participants were included in the asthma group for the study.

Healthy controls

Healthy control participants (n=78) were recruited from 6 different schools. In addition, one participant was the son of a colleague at the CFS service at the Maudsley Hospital, and another, the sister of a colleague.

A further 126 schools were contacted but contact or permission was never fully established. Of the 7 schools originally agreeing to take part (one school withdrew), a total of 1228 letters were sent out to young people at the schools. Ninety-seven potential participants replied to the letters to take part in the study. Seventy eight participants remained and took part in the study.

Another school agreed to be involved initially and 19 participants agreed to be contacted. The school later withdrew consent for involvement and so these participants

were never seen or contacted. The school found they were too busy to accommodate any involvement.

A letter was sent to the participating schools (see appendix 6, page 394) along with the information sheet for healthy controls (see appendix 7, page 395). This was followed up by a phone-call to the school with either the head teacher or the SENCO (Special Educational Needs Co-ordinator) contacted. Those schools that granted permission for recruitment consented to information sheets going to all pupils at the school. They were sent home via form tutors. Families interested in taking part returned the contact details form (appendix 4, page 390) in the envelope provided. They were given a choice of being seen at the CFS service or the school in a pre-arranged meeting room. This option was on the contact details form. Appointments were then made to suit the adolescent and their families, when in agreement with the school day and timetable. The majority (n=75) were seen at school and the remainder at the CFS service at the Maudsley Hospital (n=3).

Pathway through the study

The Mini International Neuropsychiatric Interview for children and adolescents (MINI) (Sheehan *et al.*, 1998) was conducted with adolescents attending for initial assessment at the CFS service. This was done routinely, outside of the study, to ensure that co-morbid psychiatric disorders had been adequately assessed. At this point, they also returned the questionnaires that had been posted out with their appointment letter. The

adolescents in the other 2 groups returned the questionnaires when they attended to complete the experimental tasks.

At 8 weeks the questionnaire follow-up data was collected. The questionnaires were mailed out to CFS patients, healthy control participants and their parents. They were either to be returned by post or brought to their first treatment session (CFS only).

To ensure the questionnaire data was collected, a systematic approach was adopted. If participants did not return their questionnaires within a month of being mailed they were called to remind them and they were sent a second questionnaire through the post. The questionnaires were also emailed where possible. If after 3 months the questionnaires were not received then the data for that participant was coded as missing. No questionnaires were received after this time point. See table 2.2 and 2.3 for a summary of the data collected at each stage of the study. All self-report questionnaires used can be found in appendix 8 (page 397). They are described in full in chapters 3 and 4.

Table 2.2: Clinical questionnaire measures used at each time point for the adolescents

Baseline	**8-week follow-up**
Mini International Neuropsychiatric Interview for children and adolescents (MINI; Sheehan et al., 1998)*	
Demographic information	
Chalder fatigue questionnaire (CFQ; Chalder et al., 1993)	✓
Physical functioning scale of the SF-36 (Ware, 1993)	✓
Work and social adjustment scale (WASA; Mundt, 2002)	✓
Child and adolescent perfectionism Scale (CAPS; Flett et al., 1997)	✓
Social desirability scale (SDS; Crandall, Crandall & Katkovsky, 1965)	
Insomnia scale (Abdel-Khalek, 2004)	✓
Cognitive behavioural responses questionnaire (CBRQ; Moss-Morris & Chalder, 2003)**	✓
Beliefs about emotions scale (BES; Rimes & Chalder, 2010)	✓
State-trait anxiety inventory for children (STAI-c; Spielberger, 1973)	✓
Eysenck personality questionnaire (EPQ-R Short form; Eysenck, Eysenck & Barrett, 1985)	
Frost multi-dimensional perfectionism scale (FMPS; Frost et al., 1990)	
Pediatric quality of life scale (PEDS QoL 4.0; Varni et al., 1999)	
Children's depression inventory (CDI; Kovacs & Beck, 1977)	✓
Social phobia and anxiety inventory for children (SPAI-c; Biedel, Turner & Morris, 1995)	✓

* CFS participants only

** Chronic illness groups only

Table 2.3: Clinical questionnaire measures used at each time point for the mothers

Baseline	**8-week follow-up**
Demographic information	
Chalder fatigue questionnaire (CFQ; Chalder et al., 1993)	✓
Physical functioning scale of the SF-36 (Ware, 1993)	
Cognitive behavioural responses questionnaire (CBRQ; Moss-Morris & Chalder, 2003)* **	✓
Beliefs about emotions scale (BES; Rimes & Chalder, 2010)	✓
Eysenck personality questionnaire (EPQ-R short form; Eysenck, Eysenck & Barratt, 1985)	
Frost multi-dimensional perfectionism Scale (FMPS; Frost et al., 1990)	
Pediatric quality of life scale (PEDS QoL 4.0; Varni., 1999)*	
Hospital anxiety and depression inventory (HADS; Zigmond & Snaith, 1983)	✓
SCORE40 (Stratton et al., 2010)	
Young's schema questionnaire self-sacrificing subscale (YSQ; Young, 1994)	
General health questionnaire (Goldberg, 1972)	✓
Family response questionnaire (Cordingley et al., 2001)	
Adolescent autism spectrum quotient (AQ; Baron-Cohen et al., 2001) *	
Affective style questionnaire (ASQ; Hofmann & Kashdan, 2010)	
World health organisation 5 (WHO-5, WHO, 1998)	

An * denotes the questionnaires mothers completed with regard to the child. All other measures they complete about themselves or the family

** Chronic illness groups only

Main contributory factors

Based on the literature review (chapter 1), the main contributory factors measured here were physiological, psychological (including behaviour) and social factors. Of the physiological factors heart rate (HR), heart rate variability (HRV) and cortisol have been measured before using different paradigms to those used in this thesis. Skin conductance response (SCR) was also measured. This has not been measured in

adolescents (or adults) with CFS before. These factors were investigated experimentally during a one-off task session. The psychological factors included cognitive responses to symptoms, unhelpful beliefs about expressing emotions, mood and personality factors. The personality and mood factors have been discussed previously, and this study seeks to replicate the findings to add strength to the current literature. Unhelpful beliefs about emotions and cognitive and behavioural responses to symptoms (e.g. negative beliefs about engaging in activity or all or nothing behaviour) were new lines of enquiry. Finally, social factors include social support and parenting, with both child and parent perceptions measured through questionnaires.

Potential confounders

Confounders can be defined as independent explanatory factors that are associated with the dependent variable and with the independent variable (Hennekens & Buring, 1987). They can obscure the true relationship between a risk factor and the outcome being studied by leading to either over- or under-estimation of the association being tested if they are not taken account of in the design or statistical analysis stage.

a) Demographic variables

Age, sex, ethnicity and IQ are all potential confounders. These variables were all recorded and comparisons between groups made. Where there were significant differences between the groups on these demographic variables, analyses were completed controlling for the potential confounders to check whether it could explain some of the findings. Details are discussed where appropriate.

b) Anxiety and depression

These are not being labelled as confounders. However as described in chapter 1, the symptom overlap between fatigue, anxiety and depression means it is important to check that depression and anxiety are not explaining the results. All analyses were conducted first without controlling for anxiety and depression and subsequently controlling for anxiety and depression as identified by the questionnaires (appendix 8, page 397).

Maximising data collected

To ensure maximum data was collected at both time points good communication links were established with the relevant teams. Clinical team meetings at King's College London CFS Unit and at Great Ormond Street Hospital (GOSH) were attended. The study protocol was presented to all teams involved. Updates on recruitment were presented to the teams on a regular basis.

Contact logs (see appendix 5, page 393) were devised to ensure that contact details for all participants and their families were available. This reduced the number of people failing to attend the appointment for the experimental tasks, as well as the number of missing questionnaires. All participants were sent a 'thank you' letter after the task session, reminding them that they would be sent follow-up questionnaires in 8 weeks for completion. As detailed in the information sheet, following completion of the study all participants received a £10 HMV voucher.

Power Calculations

Power calculations were performed a priori based on data from Coddington and Chalder (2003) for the cross sectional study. With a power of 80% and alpha of 0.05, the sample size estimate was 29 participants in each group. The proposed studies therefore include at least 30 participants in each group to achieve 90% power to detect a difference between groups. The power calculations were based on the Chalder Fatigue Questionnaire, with an effect size $p < .005$.

The numbers were increased for the prospective study. Ten participants are generally required per predictor variable. A larger sample of 80 participants was therefore agreed a priori for the prospective study. 78 healthy adolescents and 85 adolescents with CFS were recruited to take part.

Levels of attrition were carefully monitored. It is generally accepted that loss to follow up of less than 5% is of little concern and does not result in bias.

Statistical analyses

IBM SPSS Statistics 20 was used for data entry and subsequent statistical analyses. All subjects were given a unique identifier. All data was checked with discrepancies corrected.

It was anticipated that missing data could prove problematic as much of the data was collected by questionnaire. If participants did not return their questionnaires despite calls and additional mail-outs then these cases were marked as missing. This did not exclude them from the study, and the rest of their data was still used. When there was 25% or less of data missing from individual questionnaires they were replaced by the

mean of the remaining scale items and total scale scores calculated thereafter (pro-rating).

Statistical methods are described in more detail with each study chapter. However, the main testing method for questionnaires (both child and parent) was one-way ANOVAs for baseline data as the data met assumptions for parametric analyses. The experimental task analyses consisted primarily of ANOVAs, chi-squared and correlation analyses. For the prospective study, univariate logistic regression was used as well as multivariate regression.

For the physiological measures, the measurement of heart rate (HR), heart rate variability (HRV) and skin conductance response (SCR) is described in chapter 6. Analysis consisted of repeated measures ANOVAs and further one-way ANOVAs to explore the data. For the cortisol analysis, area under the curve was used and is described in detail in chapter 7.

Methods of dealing with missing data

There are several possible methods for dealing with missing values in research, with almost universal agreement to their strengths and weaknesses. One important consideration is why the values are missing.

Rubin (1976) defined missingness. If the fact that data are missing does not depend upon any values, or potential values, for any of the variables, then data are said to be missing completely at random (MCAR). Little (1998) has provided a statistical test of the MCAR assumption. His MCAR test is a chi-square test. A significant value

indicates that the data are not MCAR and the missing data cannot be substituted with the predicted value (e.g. mean).

Pickles (2005) suggested that any observation on a variable is as likely to be missing as any other, if the data is MCAR. If you are going to have missing data, this is the ideal case because treatment of the existing data does not lead to bias in the estimated parameters. It may lead to a loss in power, but it won't lead to biased parameter estimates. To avoid the loss in power, data is often pro-rated. Pro-rating the data using mean / mode values is very commonly used, but one must acknowledge the uncertainty of the inputted values.

Alternatives of types of missing data include, data missing at random. This is when the probability of missing data on a variable, (Y), is not a function of its own value after controlling for other variables in the design. Also, data missing not at random, if either of the above two classifications are not met.

The most common approach to missing data is to simply omit those cases with missing data and to run the analyses on what remains. This approach is usually called list-wise deletion, but it is also known as complete case analysis. Although list-wise deletion often results in a decrease in the sample size available for the analysis, it does have important advantages. In particular, under the assumption that data are missing completely at random, it leads to unbiased parameter estimates.

It is also possible to complete pairwise deletion. Under this approach each element of the inter-correlation matrix is estimated using all available data. This is not a widely recommended method. A final option is to use the mean value as a substitution, always applying caution to increased bias.

In this study

In the current study, the Little's Missing Completely at Random test was not significant, suggesting that the data were indeed missing completely at random. There was no bias. It is suggested that the questions were missed by participant error. Missing values were inputted with replacement values to treat them as if they were observed. The replacement value used was the mean of that scale (pro-rating). This was considered justified as the values can be considered to be related. It allows for complete case analysis methods. Importantly, values were only inputted for missing variables, never for missing scales in order to minimise bias in the analysis. However, this method does reduce the variability in the scale.

As a safety check for the data, all data was analysed using only the available data (i.e. list-wise deletions, not pro-rated using the mean values), as well as using the mean substitution method. All results remained the same.

For those participants that did not complete the scale at all, they were coded as missing (a value of 999 in the database). This would be the only acceptable method for an entirely missing scale. Here, in preliminary analyses, as would be recommended, the participants who did not complete scales were compared with those who did. There were no mean differences between groups. A point to note here is that this study had a very low percentage of missing questionnaire completion and the author can feel confident in the rigorous methods of data collection used.

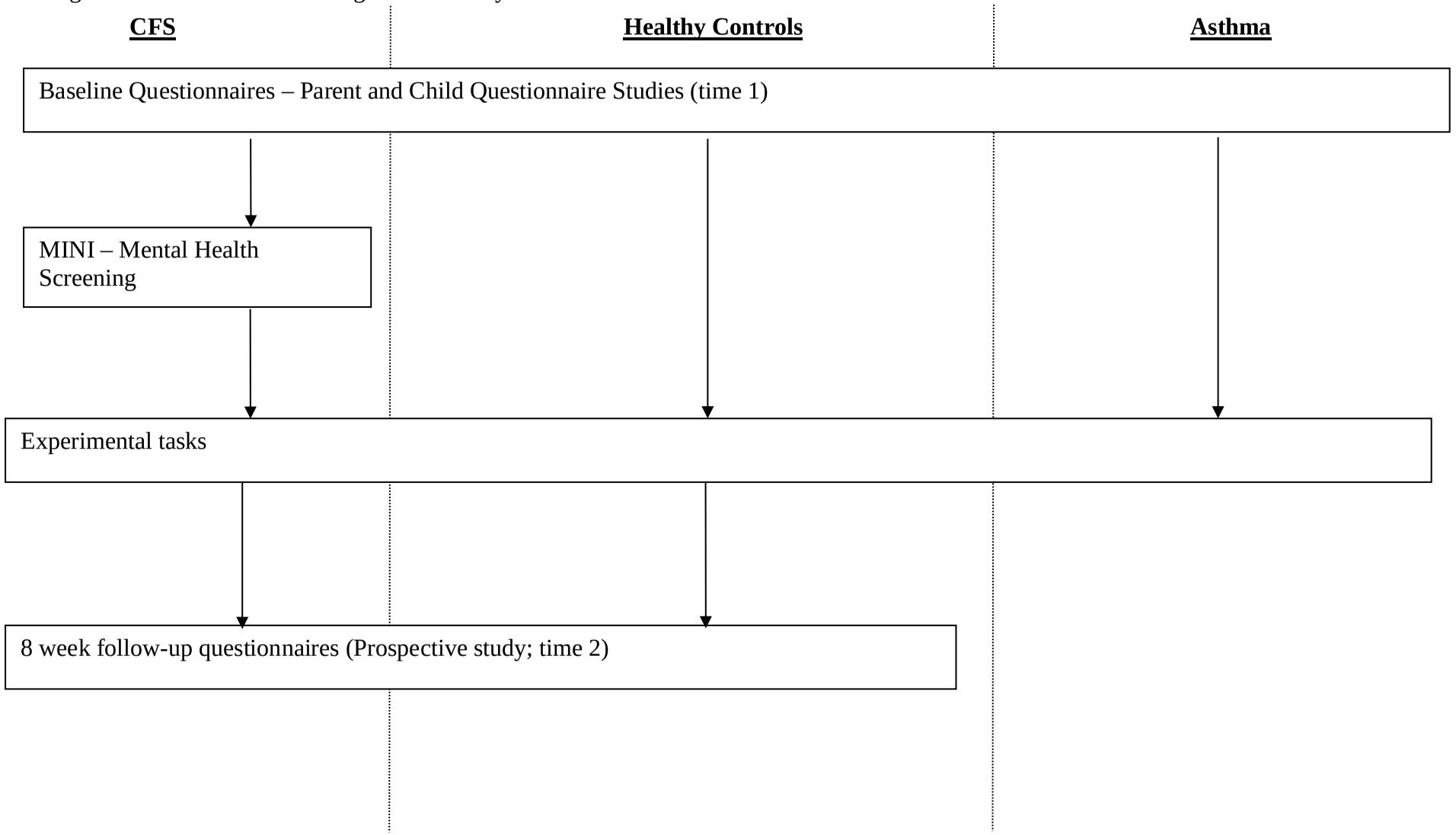
Outline of study

Figure 2.1 (page 84) presents an overview of the different stages of the study. It details which participants completed each part of the project. These aspects are addressed in subsequent chapters.

Summary

The overall objective of this thesis was to investigate various factors hypothesised to contribute to the development and perpetuation of CFS in adolescents. A prospective case-control design was chosen because the prospective aspect of the study allows an investigation into the directionality between associated factors. The measures selected for the analysis in this thesis were based on the best evidence to date, a theoretical model of CFS and to allow for testing of a priori hypotheses. The subsequent chapters will describe the individual studies, results and conclusions. These lead to an evidence based model of CFS in adolescents presented in chapter 9.

Figure 2.1: Overview of the stages of the study



Chapter 3: Cross-sectional questionnaire study

Synopsis

The aim of this chapter is to first describe the main clinical characteristics of the CFS group according to DSM-IV criteria for psychiatric disorder. It also compares adolescents with CFS with an illness control group (asthma) and a group of healthy adolescents on a range of questionnaire measures.

The primary hypothesis was that the CFS group would have significantly higher scores on measures of unhelpful beliefs and behaviours in response to symptoms than the asthma group. It was hypothesised that the CFS group would have significantly more negative beliefs about emotions, higher neuroticism, perfectionism, social desirability, and lower extraversion than the control groups. Further, it was hypothesised that the adolescents with CFS would have worse physical functioning, worse school and social adjustment, worse quality of life as well as higher scores on measures of fatigue, anxiety and depression than the other 2 groups.

Forty-four (51.8%) of the adolescents with CFS met DSM-IV criteria for a psychiatric disorder assessed by the Mini International Neuropsychiatric Inventory. The most common disorders were depression and anxiety, and consistent with this, the CFS group had significantly higher scores on questionnaire measures of symptoms of depression and state-trait anxiety than the control groups. The CFS group scored significantly higher on all measures of unhelpful beliefs and behaviours in response to symptoms than the asthma group. As predicted, the CFS group had higher scores on measures of neuroticism, social desirability, fatigue, sleep disturbance and school and social adjustment than the other two groups. The CFS group also had significantly worse physical functioning and worse rated quality of life as well as lower scores for

extraversion. The CFS group had significantly higher scores for doubts about actions (subscale of negative perfectionism) than the other two groups. The CFS group had significantly higher scores on the sleep scale than the other two groups. There was also a significant difference between the groups on IQ. The CFS group had significantly lower IQ than both of the other two groups. In addition, mothers completed the autism spectrum questionnaire rating social skills in their child. The overall score on the autism spectrum quotient was significantly higher in the CFS group, with lower ratings of their child's social skills, attention switching and communication by mothers of the CFS adolescents compared to the other two groups. The results and clinical implications of the findings are discussed.

Introduction

The aetiology of CFS in adolescents is uncertain (Browne & Chalder, 2006). However, it is likely that both the development and perpetuation of the disorder are due to an interaction of cognitive, behavioural, physiological, affective and social factors (Chalder *et al.*, 2002). Theories informing therapeutic options for adolescents with CFS have been broadly based on models and research evidence in adults (Wessely *et al.*, 1989). In this chapter, potential predisposing and perpetuating factors will be investigated.

Beliefs and behaviours in response to illness

Wessely *et al.* (1989) suggested that although fatigue may often have been initially triggered by an infection, other factors may then act to maintain the condition. Wessely et al. propose that the individual starts to reduce their activity levels in an understandable attempt to feel less fatigued, but in fact their exercise tolerance worsens. Fatigue subsequently increases when they try to do more. Beliefs such as 'there must be something seriously wrong with me' and 'if I continue with this activity I will end up feeling worse', contribute to activity reduction and avoidance. The individual ends up in a vicious cycle of unhelpful beliefs about activity, activity reduction, exercise intolerance, fatigue and disability. This can contribute to the development of distress, sometimes anxiety or depression of clinical severity, which in turn causes more fatigue and other physical symptoms (Chalder *et al.*, 2002).

Using the Cognitive Behavioural Responses Questionnaire (Skerrett & Moss-Morris, 2006) those specific constructs (which are central to the cognitive behavioural model) will be investigated and possible differences between the chronic illness groups will be

examined. More specifically, these include negative beliefs about engaging in activity, embarrassment avoidance, symptom focusing, catastrophising and damage beliefs as well as all or nothing behaviour and avoidance of activity behaviours. These beliefs and behaviours about illness have been shown to be elevated in a CFS population in adults, specifically as maintaining factors. Most prominently, avoidance of activity or negative beliefs about activity have been associated with maintaining the condition in adults (e.g. (Sharpe *et al.*, 1992)). Symptom focusing was cross-sectionally associated with a worse quality of life in adolescents (Gray & Rutter, 2007). Clinical experience has also led researchers to suggest all or nothing behaviours are at the core of a model of CFS in adolescents (Chalder *et al.*, 2002).

Personality and other factors

Unhelpful beliefs about emotions

Unhelpful beliefs about emotions are part of the Surawy et al. model of CFS in adults (Surarwy *et al.*, 1995) and have not before been investigated in adolescent CFS. Surawy and colleagues suggest that unhelpful beliefs about emotions may contribute to CFS by leading people to try to hide their emotions and not seek support. This can lead to continued distress, resulting in increased levels of fatigue. People with unhelpful beliefs about emotions may also attempt to suppress or ignore unwanted emotions which may prevent adequate emotional processing and increase distress. Rimes and Chalder (2010) devised the Beliefs about Emotions Scale (BES) (Rimes & Chalder, 2010). They reported that adults with CFS had more negative beliefs about experiencing and expressing emotions compared to a healthy control group. Given the findings in adults,

it is hypothesised that the young people with CFS in this study will have more negative beliefs about expressing emotions than the control groups.

Personality

Personality factors in adolescents with CFS were discussed in the literature review (pg 33). The key findings suggest that adolescents with CFS are more likely to generally experience more personality difficulties. There is evidence from cross-sectional studies that personality characteristics such as a tendency for the individual to be conscientious or to exhibit certain traits such as rigidity or sensitivity may play a role in adolescent CFS (Rangel *et al.*, 2003; Rangel *et al.*, 2000a). These may have arisen from a genetic vulnerability and / or early life experiences (Heim *et al.*, 2006). It is likely that these traits act as predisposing factors in CFS as they are assumed to be persistent personality characteristics. In this study, neuroticism, extraversion and social desirability will be compared in the 3 groups.

A further factor under investigation is perfectionism. Cognitive behavioural theories of CFS in adults (Surarwy *et al.*, 1995) and adolescents (Lloyd *et al.*, 2012) propose that perfectionism, or excessive high standards, lead to increased fatigue levels. Surawy and colleagues reported that adults with CFS in their clinic tended to have high standards for performance, personal conduct and were very responsible. There is an assumption that the failure to meet these self-expectations would indicate a disappointment. It could lead to an increased effort adding to already increased levels of fatigue. A repeated experience of not achieving goals will reinforce negative beliefs that they are suffering an illness that they cannot overcome causing further distress and avoidance of activity (Surarwy *et al.*, 1995). It is proposed that this may be a vulnerability factor and also act

as a maintaining factor in CFS. This is the first study to investigate perfectionism in adolescents with CFS. Studies investigating perfectionism in adults remain inconclusive, with some studies finding higher levels of perfectionism in adults with CFS compared to healthy controls (White & Schweitzer, 2000). Others report no such association (Wood & Wessely, 1999).

In a similar context, there is consistent, cross-sectional evidence of high expectations in young people with CFS in comparison to control groups. Inaccurate expectations and unrealistic perceptions were reported with regards to fatigue (Garralda & Rangel, 2001) and activity levels (Fry & Martin, 1996), in adolescents with CFS. Both adolescents with CFS and their parents were found to significantly underestimate the adolescents' current activity levels and had higher expectations of their post-CFS activity levels than was realistic for children of that age (Fry & Martin, 1996). High standards appear to be problematic in a general sense across aspects of life (Garralda & Rangel, 2001; Godfrey *et al.*, 2009).

Mood / co-morbidities

The literature to date provides strong evidence of increased rates of psychiatric co-morbidity in adolescents with CFS compared to healthy or ill control groups (e.g. (Smith *et al.*, 1991)). Concurrent psychiatric disorders (mostly depressive disorders or anxiety disorders) are reported in between a quarter to a third of young people with CFS ((Smith *et al.*, 1991) – community sample; (Vereker, 1992) – specialist treatment centre sample; (Walford *et al.*, 1993) – attending an immunology clinic for CFS). Ter Wolbeek *et al.* (2011) reported that vulnerability to develop fatigue and associated symptoms in young adulthood can to a certain extent be identified already, years before

the manifestation of complaints. They found that in young people who experienced a notable increase in fatigue, fatigue development was preceded by emotional problems and CFS-related complaints during adolescence. The nature of the association is unknown and it is possible that genes, early life experiences and learned psychological responses act individually or together (e.g. via differences in hypothalamic pituitary adrenal axis responding) as risk factors for both psychiatric disorders and CFS.

Few studies (n = 6) have used semi-structured interviews to make clinical diagnoses of anxiety and / or depressive disorders (Garralda & Rangel, 2005; Garralda *et al.*, 1999; Heim *et al.*, 2009; Rangel *et al.*, 2003; Rangel *et al.*, 2000b; Smith *et al.*, 1991). This current study uses a routine clinical interview (MINI) to assess psychiatric co-morbidity in the CFS group specifically as well as the frequently used questionnaire measures.

Fatigue and impairment

Excessive fatigue, impaired physical functioning and school and social adjustment are key problems for patients with CFS (e.g. (Patel *et al.*, 2003)). Decreased quality of life in adolescents with CFS has not been systematically investigated. Quality of life was discussed in relation to a study investigating functional impairment in CFS (Solomon *et al.*, 2003). This population based study reported significant impairment in the CFS group in comparison to healthy controls. If there is a better understanding of specific problems related to quality of life in CFS (e.g. school functioning), this may aid our understanding of how best to manage the illness.

Attributions of illness

According to Robbins and Kirmayer (1991) the experience of symptoms can be attributed to three different sets of factors. These are somatic attributions (where the

symptoms are viewed as a sign of physical abnormality), psychological attributions (emotional upset), and normalising attributions (where there are external events such as a change in the environment or one's behaviour). In the cognitive behavioural model, attributing fatigue to an on-going virus would be a somatic attribution. A psychological attribution would be to attribute the symptoms to stress. Adolescents with CFS have a tendency to make somatic attributions for their symptoms (Garralda & Rangel, 2001) and are less likely to make psychological attributions for symptoms (Rangel *et al.*, 1999). It is possible that this attributional style is an important predictor of the illness itself.

Maternal report about the child

Adolescents with CFS often report problems with attention (Haig-Ferguson *et al.*, 2009). Mothers of adolescents with CFS, asthma and healthy controls will be asked to complete the Autism Spectrum Quotient (AQ) (Baron-Cohen *et al.*, 2001). No link was being made between autism and CFS. The subscales of the AQ do however measure constructs reported to be difficult in adolescents with CFS. These are largely related to social difficulties. In the Haig-Ferguson *et al.* (2009) study, children, parents and teachers alike described problems with focussed attention, sustained attention, recall and stress in the adolescents with CFS. These factors could be considered to have an impact on one's performance. This scale is included here as it is an indication of characteristics in the child. It is a maternal report.

These traits may predate the CFS, making the child more vulnerable to the condition, perhaps due to finding common situations more stressful due to increased social anxiety and higher levels of neuroticism. It will also link to school attendance. The child may feel isolated due to time missed from school.

Overall chapter objective

The main research objective of this chapter was to compare the psychological and behavioural characteristics of adolescents with CFS, adolescents with asthma and healthy controls using self-report measures and a standardised psychiatric diagnostic interview.

Hypotheses

Beliefs and behavioural responses to symptoms

On the cognitive behavioural responses questionnaire, the CFS group will have significantly higher scores on subscales measuring negative beliefs about engaging in activity, catastrophising beliefs, damage beliefs, embarrassment avoidance, symptom focusing, all or nothing behaviour and avoidance of activity behaviours than the asthma group.

Personality and related factors

On the personality measures, the CFS group will have significantly higher scores of neuroticism (Eysenck personality questionnaire; EPQ), perfectionism (child and adolescent perfectionism scale; Frost multi-dimensional perfectionism scale), and the social desirability scale, as well as lower scores on the extraversion scale of the EPQ, when compared to the other two groups.

The CFS group will have significantly more unhelpful beliefs about the acceptability of experiencing or expressing negative emotions than the other two groups.

Mood / Co-morbidities

The CFS group will have higher rates of DSM-IV psychiatric disorder than population norms.

The CFS group will have significantly higher scores for symptoms of depression on the children's depression inventory than the other two groups. The CFS group will also have significantly higher scores for anxiety symptoms on the state-trait anxiety inventory for children and the social phobia and anxiety inventory than either of the other two groups.

Quality of life

The CFS group will have a significantly lower score on the Peadiatric Quality of Life scale than the other two groups, indicating a worse perception of life quality in this group.

Maternal report about the child

The mothers of the CFS patients will rate their child significantly higher on subscales of the autism spectrum quotient reflecting more struggles socially (e.g. in communication) in this group than the other two groups.

Method

Design

This is a cross-sectional questionnaire study. This design includes 3 participant groups; 85 adolescents with CFS, 31 adolescents with asthma and 78 healthy controls. The use of an illness control group as well as a healthy control group adds strength to the study

by assessing whether any difference between groups is due to chronic illness generally, or CFS specifically.

Procedure

The CFS group were recruited continuously from referrals to Great Ormond Street Hospital (GOSH) or the CFS service at Kings College Hospital. The asthma and healthy control groups were opportunity samples. They replied to a letter about the study (as described further in the participants section of chapter 2).

The Mini International Neuropsychiatric Interview for children and adolescents (MINI-KID) was completed face-to-face to screen for any psychiatric disorders that were part of the study exclusion criteria and to help characterise the CFS participants only. The author completed the MINI interview with the adolescents at their initial assessment as part of routine clinical practice. The screening interview was completed over the telephone with 5 participants. The outcome was verified by checking the clinical notes.

All participants in all 3 groups completed the self-report questionnaires (see appendix 8, page 397). These were sent to the participant and their parents with a confirmation letter of their appointment. They were asked to return the completed questionnaires at their visit – either to the diagnostic assessment for the CFS participants, or the task session for the other 2 groups. Participants were asked to answer the questions as honestly and as quickly as possible. It was made clear that if the participants found it hard to keep their mind on the statements, they could take a short break; completing the questionnaires over a day or two if needed. The questionnaire was confidential and was not shown to anyone. The questionnaires take approximately 30 minutes to complete in total.

All questionnaires were completed by each group, except the cognitive behavioural responses questionnaire (CBRQ; described later) which was completed by the CFS and asthma groups only. This is because the scale specifically focuses on beliefs and behaviours in response to symptoms of illness.

Measures

Mini International Neuropsychiatric Interview for children and adolescents (MINI-KID; DSM-IV) (Sheehan *et al.*, 1998)

The MINI-KID is a brief, structured interview for the major Axis I psychiatric disorders in DSM-IV and ICD-10. It can be administered in between an average of 12 and 19 minutes (Sheehan *et al.*, 1998). The psychiatric disorders it covers are: Major Depressive Episode, Dysthymia, Suicidality, (Hypo) Manic Episode, Panic Disorder, Agoraphobia, Separation Anxiety, Social Phobia, Specific Phobia, Obsessive Compulsive Disorder, Posttraumatic Stress Disorder, Alcohol Dependence, Non-alcoholic Substance use Disorders, Conduct Disorder, Oppositional Defiant Disorder, Psychotic Disorders, Anorexia Nervosa, Bulimia Nervosa, Generalized Anxiety Disorder, Adjustment Disorders, ADHD and Pervasive Developmental Disorder. The MINI has previously been used in studies of CFS in adults (Caseras *et al.*, 2008). It has been shown to have reliability and validity compared with other pre-existing diagnostic interviews such as the schedule for affective disorders and schizophrenia for school aged children - present and lifetime version (K-SADS-PL) (Kaufman *et al.*, 1997) in children and adolescents (Sheehan *et al.*, 2010).

Demographic Information

Demographic information was collected on all participants. This included age, gender, main carer, ethnicity and time at school in full days and half days (this was then calculated into a percentage for analyses). Participants were also asked about their medical history. Patients with CFS or asthma were asked to complete a further set of questions about onset; how long ago they noticed the onset of their symptoms. Additionally, the CFS patients completed a questionnaire to assess whether they met the CDC criteria for CFS. They were also asked what they **attribute the cause of their symptoms** to as well as the time they believed it would take to recover.

Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999)

The Wechsler Abbreviated Scale of Intelligence was used as a brief measure of the participants' IQ levels and was conducted at the same time as the experimental tasks (chapter 5). This was included to assess whether there were any differences between the groups in terms of IQ and to assess whether IQ affected performance. It is reported in this chapter as a sample characteristic. The subscales completed were the Vocabulary and Similarities sub-tests for verbal IQ, and the Block Design and Matrix reasoning for performance IQ. These make up the marketed WASI. The subscales took no longer than 30 minutes to complete in total.

Beliefs and behaviours in response to symptoms; Chronic Conditions Only (CFS group and Asthma group)

This scale was devised to investigate patients' cognitive and behavioural responses to symptoms. The CBRQ was devised and validated in a CFS population (Knudsen *et al.*, 2011; Moss-Morris & Chalder, 2003). This is the first time it has been used in adolescents with CFS. The measure includes 41 items, split into 5 cognitive subscales and 2 behavioural subscales; the cognitive – negative beliefs about engaging in activity (7 items) including "I am afraid that I will make my symptoms worse if I exercise", catastrophising (4 items) including "I will never feel right again", damage (5 items) including "Symptoms are a signal that I am damaging myself", embarrassment avoidance (6 items) including "I am ashamed of my symptoms" and symptom focusing (6 items) including "When I experience symptoms, I think about them constantly". The two behavioural subscales are all-or-nothing behaviour (5 items) including "I tend to overdo things when I feel energetic" and avoidance of activity behaviours (8 items) including "I stay in bed to control my symptoms". Cronbach's α for each of the subscales is reported in table 3.1. The values for Cronbach's α are all high which indicates a high level of internal consistency for the scale (.752 - .906).

Table 3.1: Internal consistency of the subscales of the CBRQ (Cronbach's alpha)

Subscale	Cronbach's Alpha (α)
Overall Total	.850
Negative beliefs about engaging in activity	.816
Catastrophising	.816
Damage	.752
Embarrassment avoidance	.883
Symptom focusing	.906
All or nothing behaviour	.856
Avoidance of activity behaviour	.822

Personality and Other Factors

Beliefs about Emotions Scale (BES) (Rimes & Chalder, 2010)

This questionnaire was designed to assess beliefs about the unacceptability of experiencing or expressing negative emotions. This is a 12-item scale which includes items such as "It is a sign of weakness if I have miserable thoughts" and "To be acceptable to others, I must keep any difficulties or negative feelings to myself". Response options are totally agree, agree very much, agree slightly, neutral, disagree slightly, disagree very much and totally disagree. Responses are scored 6, 5, 4, 3, 2, 1, and 0 respectively. Higher scores indicate greater endorsement of unhelpful beliefs about emotions. It has been used with adults with CFS (Rimes & Chalder, 2010) and the scale was found to have high internal consistency (0.91). The cronbach's alpha in this study was 0.895.

Eysenck Personality Questionnaire (EPQ-R Short-form – neuroticism and extraversion only) (Eysenck *et al.*, 1985)

The EPQ is a self-report questionnaire based on Eysenck's theory of personality. The EPQ measures two personality tendencies; neuroticism and extraversion. The 24-item scale is a dichotomous scale and respondents indicate a true or false response to each item. The neuroticism scale (N scale) measures the degree to which the individual is predisposed to experience negative affect. An example of a question on the N scale is "do you often feel lonely?" or "are you a worrier?" The extraversion scale (E scale) assesses the degree to which individuals are sociable, active and impulsive. An example of this subscale includes "are you a talkative person?" or "do you enjoy meeting new people?"

This measure is a short form of the full EPQ, but has been reported to have similar psychometric properties as the full scale. The reliability of the EPQ-R (Eysenck *et al.*, 1985) has been examined in multiple studies. In these studies, the neuroticism and extraversion scales of the EPQ-R show very good internal consistency (Cronbach α between .80 and .90) and good consistency over time (with test-retest reliability ranging from 0.85 to 0.94). The reliability of this scale in this study, as measured by the Cronbach's alpha was .796 for the N scale and .870 for the E scale.

Child and Adolescent Perfectionism Scale (CAPS) (Flett *et al.*, 1997)

The CAPS was designed to measure self-oriented and socially prescribed perfectionism. Self-oriented perfectionism includes having strong motivations for oneself to be perfect, unrealistic standards for oneself, all or nothing thinking and maintaining a focus on one's own flaws. Socially prescribed perfectionism is an interpersonal dimension

involving perceptions of one's need and inability to meet the standards and expectations imposed by others. It is the belief that others have unrealistic standards and expectations for one's own behaviours.

The CAPS is a 22-item self-report scale. Items are rated on a 5 point likert scale from 1 (false-not true at all of me) to 5 (very true of me) and higher scores indicate greater perfectionism. In this study, the Cronbach's alpha was .891. Twelve items refer to the self-oriented perfectionism and 10 items socially prescribed. Four of the items are reverse scored.

Frost Multi-dimensional Perfectionism Scale (FMPS) (Frost *et al.*, 1990)

The FMPS is a 35-item multidimensional scale to measure perfectionism. Setting excessively high standards is the most prominent feature of perfectionism (Pacht, 1984). The scale was first tested on 72 female undergraduate students, where students were asked to complete the self-report questionnaires in small groups. The scale has an overall perfectionism score as well as 6 subscales; concern over mistakes, personal standards, parental expectations, parental criticism, doubts about actions and organisation. This is a widely used scale in personality and clinical research (e.g. (Brown *et al.*, 1999)). Each of the dimensions has been shown to be reliable and valid (Frost *et al.*, 1990). The first five subscales are seen to represent the core dimensions of the FMPS, with organisation found to be only loosely related to the other scales. Therefore, organisation is not included when calculating the total overall score. The scale can also be split into negative (doubts about actions, concern over mistakes, parental expectations and parental criticism) and healthy (organisation and personal standards) perfectionism.

The concern over making mistakes subscale has been used to distinguish perfectionists from those who set high standards for themselves because they are highly competent and successful (Frost *et al.*, 1990). The second dimension involves the setting of personal standards of performance. It is the concept of setting excessively high standards that cannot be satisfactorily met. This is a concept recognised amongst clinicians working with young people with CFS (e.g.(Lloyd *et al.*, 2012b)). The doubt about actions subscale focuses on the tendency to doubt the quality of one's performance; how well one would be able to do something. The following two subscales are concerned with the perceptions of parents' attitudes; whether parents have high expectations of the child or are perceived as being overly critical of the child. Organisation is the separate subscale, but is included as it reflects the order and orderliness that is oft associated with perfectionism (Hollender, 1965). Although not widely used in adolescents, the internal consistency in this study showed all psychometric properties of the scale were well in line with the original (Parker, 1989). The internal consistency was between .797 and .932 for the individual subscales.

Social Desirability Scale (Crandall *et al.*, 1965)

This is a 48-item scale which assesses social desirability. Social desirability is the tendency to respond to questions in a way that would be considered favourable to others rather than what is necessarily true to them. It may be over-reporting good behaviour or under-reporting bad behaviours (e.g. (Nederhof, 2006)). It was originally used on a group of 956 American school children (Grade 3 – 12) to identify persons with high social desirability. The items all concern personal attitudes and traits and list experiences that most children have at one time or another e.g. "I am always respectful

of others". The items are all rated true or false and then scored 0 or 1 in accordance with the most socially desirable response with the maximum score being 48. The scale has been shown to be reliable and valid (Crandall *et al.*, 1965) and Cronbach's alpha in this study was 0.88.

Mood / Co-morbidities

Children's Depression Inventory (CDI) (Kovacs & Beck, 1977)

The CDI is a self-report inventory devised by Kovacs and Beck (1977) to measure symptoms of depression in children and adolescents. It is widely researched and a useful clinical tool. It is an extension of the Beck Depression Inventory (Beck *et al.*, 1961) for children and has 27 items. The CDI is considered psychometrically strong (Kovacs, 1992). Cronbach's alpha in this study was .896. Each item has 3 possible responses that are graded in severity and subsequently assigned a numerical value from 0 to 2. This gives a total score range of 0 to 54. Participants are asked to rate how they have been feeling and thinking during the last 2 weeks. The recommended clinical cut-off score for this measure is 13 or above.

State-Trait Anxiety Inventory for Children (STAI-C) (Spielberger, 1973)

The STAI-C was developed (Spielberger, 1973) to provide a reliable self-report scale for assessing state and trait anxiety for both research and clinical practice (Spielberger, 1973). The scale consists of 40 items; 20 state items and 20 trait items. The state instructions ask participants to rate on the 4 point scale the intensity of their feelings of anxiety "right now, at this moment" and the trait instructions asked them to indicate

how they generally feel by reporting the frequency of occurrence of anxiety-related feelings and symptoms. In responding to the state items, participants rated (1) not at all, (2) somewhat, (3) moderately so, and (4) very much so. The rating for the trait scale is (1) almost never, (2) sometimes, (3) often, (4) almost always, for how they generally feel. The STAI-C has been found to have acceptable validity, internal reliability and test-retest reliability (Spielberger, 1973). In this study, the Cronbach's alpha was .966. It is a scale used to make a clinical diagnosis of anxiety by professionals and has a total maximum score of 80 (20 minimum).

Social Phobia and Anxiety Inventory for children (SPAI-c) (Beidel *et al.*, 1995)

Although the STAI-C may accurately reflect the child's general distress, it provides little information about the distress in social situations. The social phobia and anxiety inventory (SPAI-C) was therefore also included in this study.

The SPAI-C was designed to specifically assess social phobia and social anxiety in children and adolescents. It is a 26-item scale with 18 items requiring multiple responses. For these items, participants were asked to differentiate the distress on the basis of their familiarity with the other individuals in the social encounter (e.g. peer or adults they know). Each statement was rated on the following 3-point scale; 0 = never or hardly ever, 1 = sometimes, and 2 = almost always or always. The scale was first used on children with either a) a diagnosis of social phobia, b) overanxious disorder, c) both social phobia and overanxious disorder, d) avoidant disorder of childhood, or e) normal controls. The 18 items requiring multiple responses are summed, and a mean score is calculated for each of these items. The SPAI-C total score is then calculated by

summing each of the 26 items. The maximum score of the SPAI-C is 52. For this measure, a recommended clinical cut-off score of 18 or above is used.

An extension of the study was then conducted by the same team (Beidel *et al.*, 1995) investigating the reliability and validity of the scale. The scale has high test-retest reliability and internal consistency. The scores on the SPAI-C successfully distinguished between the healthy control group and the socially anxious children. The Cronbach's alpha in the current study was .965.

Fatigue and impairment scales

Chalder Fatigue Questionnaire (CFQ) (Chalder *et al.*, 1993)

This is a self-rated measure of the severity of fatigue that was chosen to assess the CFS symptom characteristics of this sample. The scale has 11 items covering both physical and mental symptoms of fatigue. The individual answered each question using a 4-point scale (less/better than usual, no more than usual, more than usual, much more than usual) i.e. 0,1,2,3. These translate into binary scoring of 0 for the two items indicating lower levels of fatigue and 1 for the two items indicating higher levels of fatigue. Another scoring option is out of 33. Scores for each question are totalled, with higher scores indicating more fatigue. The CFQ has good face validity and reasonable discriminant validity (Cella & Chalder, 2010; Chalder *et al.*, 1993) and has been used in children and adolescents (e.g. (Chalder *et al.*, 2010)) with good internal consistency. More recently its psychometric properties have been explored in adolescents. The scale was found to be valid and reliable (Ridge, et al, in submission). In this study, the Cronbach's alpha was .926.

School and Social Adjustment Scale (SASA) (Mundt *et al.*, 2002)

The work and social adjustment scale (WASA) is a self-report scale to investigate patients' perceptions of functional impairment. The school and social adjustment scale (SASA) is an adapted version to suit the needs of adolescents by changing the work item to school or college (Cella *et al.*, 2011). It is a 5-item scale, all rated from 0 (not at all impaired) to 8 (severely impaired). With a maximum score of 40, the authors (Cella *et al.*, 2011; Mundt *et al.*, 2002) suggest that a score of above 20 indicates moderately severe or worse psychopathology. Scores between 10 and 20 are associated with significant functional impairment but less severe clinical symptoms and scores below 10 appear to be associated with subclinical populations. There are no specific cut off scores for case-ness, with the scale acting as a continuous scale. The authors found that the WASA had good internal consistency (i.e. Cronbach's α ranging between .70 and .90). In this study the Cronbach's alpha for the SASA was .945.

Physical Functioning Scale of the SF-36 (Ware *et al.*, 1992)

The SF-36 physical functioning sub-scale (Ware *et al.*, 1992) measures physical functioning. It helps to characterise the degree of physical impairment experienced by the participants across the groups. It is a 10-item self-report scale, with a maximum score of 100. This maximum score indicates no physical impairment. The scale is a 3-point scale ranging from 0 (not at all) to 10 (yes, limited a lot). This measure is reliable and valid and has been used in adolescents with CFS (Bell *et al.*, 2001; Chalder *et al.*, 2010; Stewart *et al.*, 1998a; Stulemeijer *et al.*, *2005*). The Cronbach's alpha in this study was .937.

Quality of Life

Pediatric Quality of Life Scale (PEDsQL 4.0) (Varni *et al.*, 1999)

The PEDsQL integrates generic core scales and disease-specific modules into one measurement system (Varni *et al.*, 1999). It was originally devised from a cancer database, to be used across pediatric populations. The PEDsQL 4.0 used in this study measures the core health dimensions delineated by the World Health Organisation. The 23-item questionnaire has 4 subscales; 1) physical functioning (8 items), 2) emotional functioning (5 items), 3) social functioning (5 items), and 4) school functioning (5 items). The instructions ask how much of a problem each of the items has been during the past 1 month. It is a 5-point response scale; 0 = never a problem, 1 = almost never a problem, 2 = sometimes a problem, 3 = often a problem, 4 = almost always a problem.

Varni *et al.* (2001) reported the reliability and validity of the PEDsQL 4.0. Most scales approached or exceeded the minimum reliability standard of 0.70 for internal consistency reliabilities. The authors also investigated the correlation between the items and descriptors of morbidity and burden of illness (e.g. school missed). The items demonstrated small to medium correlations with the number of days missed from school and the scales demonstrated differences between the groups (healthy, acute illness and chronic illness). The cronbach's alpha in this study, overall and for each subscale is shown in table 3.2.

Table 3.2: Cronbach's alpha for the PEDS QoL

Subscale	Cronbach's Alpha (α)
Overall Total	0.959
Physical functioning	0.949
Emotional functioning	0.834
Social functioning	0.813
School functioning	0.909

Insomnia Scale (Abdel-Khalek, 2004)

This is a 12-item self-report scale where items are answered on a 5-point scale. This scale is composed of two factions; difficulty in initiating sleep and maintaining sleep (sleep problems), and consequences of sleep. The scale is a 5-point scale (0 = no, 1 = a little, 2 = moderate, 3 = much and 4 = very much). For each question, participants are asked to tick the box that most applies to them. The Insomnia Scale has acceptable test-retest alpha reliabilities and good convergent validity. In this study, the Cronbach's alpha was .911.

Maternal report about the child

Adolescent Autism Spectrum Questionnaire (AQ) (Baron-Cohen *et al.*, 2001)

The mothers completed this scale by rating their child. The adolescent AQ comprises 50 questions, made up of 10 questions assessing 5 different areas; social skills, attention switching, communication, attention to detail and imagination. Each of the items scores 1 point if the respondent records the abnormal or autistic like behaviour either mildly or

strongly; abnormality – poor social skill, poor communication skill, poor imagination, exceptional attention to detail, or poor attention switching/strong focus of attention. It is a likert scale with responses 1 – 4; this is then recoded to binary scoring. The maximum score on the scale is therefore 50 with highest scores indicating traits of autism. It can quantify where an adolescent is situated on the continuum from autism to typical functioning. The Cronbach's alpha of this measure in this study was .527. The measure was used in this study to obtain a maternal report of social difficulties in the CFS population in comparison to the control groups.

Statistical Analyses

All scales were scored using Syntax for SPSS. Pro-rating was described in chapter 2, page 81. All data were explored for normality. Data was inspected visually using histograms, quantile-quantile (Q-Q) plots and box plots. No violations of normality were identified for any variables (questionnaire scores). Sample characteristics were reported for the whole sample and by group. Pearson Chi-squared tests were used to compare groups on participant demographic characteristics.

The three groups were compared for scores on each questionnaire measure used. Comparisons were undertaken using one-way independent ANOVAs (see table 3.10-3.14 for means and results on the comparisons). Post-hoc tests were Tukey's (when equal variances assumed) or Games-Howell (GH; when equal variances could not be assumed). Independent t-tests were used for the CBRQ where only the two chronic illness groups completed the questionnaire.

ANCOVAs were conducted on the significant questionnaire measures to control for anxiety and depression symptoms according to scores on the STAI and CDI respectively. Given the overlap between anxiety and depression symptoms and CFS (e.g. (Walford *et al.*, 1993)), it is warranted to control for these factors to see if they may explain some of the finding. All findings from these analyses are in appendix 9 (page 434).

ANCOVAs were also conducted to control for IQ differences on the significant questionnaire measures, according to the overall IQ score. It is justified to control for IQ as it may explain some of the finding as a demographic difference between the groups – a possible confounder.

Bonferoni correction was used throughout to minimise this possible error. A large number of comparisons in studies raise the possibility that some of the statistical significances are due to type 1 errors, so caution should be taken when interpreting the findings.

Results

Sample characteristics

All adolescents were aged between 11 and 18 years. Table 3.3 outlines the demographic variables of the groups and results of statistical comparisons (one-way ANOVAs or chi-square analyses). There were no significant group differences for age, sex, ethnicity or main carer.

Table 3.3: Demographic variables for all adolescents; age, sex, ethnicity and main carer

		Data			Result
Age	CFS	Mean: 14.96 (1.74)			$F(2,191) = 1.29$, $p = .277$
	Asthma	Mean: 15.00 (2.18)			
	Healthy Control	Mean: 14.58 (1.40)			
Sex	CFS	32.9% male	67.1% male		$X^2 (2) = 3.36$, $p = .186$
	Asthma	51.6% male	48.4% female		
	Healthy Control	38.5% male	61.5% female		
Ethnicity	CFS	92.9% White British	7.1% other		$X^2 (2) = 5.41$, $p = .067$
	Asthma	77.4% White British	22.6% other		
	Healthy Control	85.9% White British	14.1% other		
Main carer	CFS	60% both	38.8% mother	1.2% father	$X^2 (2) = 8.66$, $p = .070$
	Asthma	80.6% both	19.4% mother	0.0% father	
	Healthy Control	74.0% both	22.1% mother	3.9% father	

Characteristics of the CFS group

All adolescents with CFS were asked about their symptoms and impairment. Ninety-one point four per cent of the adolescents with CFS reported they suffered from moderate to severe fatigue, with 11% suffering physical fatigue only and the remaining 88.9% suffering from both physical and mental fatigue. Further, the entire CFS group suffered from fatigue 50% of the time or more as per diagnostic criteria. Ninety three point eight per cent had been fatigued for 6 months or more when they entered the study. The remaining 6.2% had been fatigued for at least 3 months which is recognised as long enough for a diagnosis of CFS in adolescents.

The adolescents were asked to report activities or actions that were substantially impaired due to their fatigue. These results are reported in table 3.4. The adolescents suffered greatest impairment in study and physical exercise, as well as leisure activities.

Table 3.4: Activities substantially impaired due to fatigue in adolescents with CFS (percentage reported)

"Does the fatigue substantially impair…?"	Yes (%)	No (%)
Work	38.3	61.7
Study	**93.8**	6.2
Physical exercise	**93.8**	6.2
Housework and home management	33.3	66.7
Self-care	33.3	66.7
Leisure activities	**80.2**	19.8
Family life	37.0	63.0

The adolescents were also asked to complete a question asking them to report symptoms (according to the Fukuda criteria (Fukuda *et al.*, 1994)). The results are displayed in table 3.5. The primary symptom of CFS is fatigue, but other important symptoms were un-refreshing sleep, muscle pain and headaches.

Table 3.5: Symptoms experienced by adolescents with CFS (percentage)

	Muscle pain	Joint pain	Headaches	Tender neck/armpit glands	Sore throats	Malaise after exertion	Poor memory	Poor concentration	Un-refreshing sleep
Yes (%)	**71.6**	56.8	**84.0**	38.3	60.5	46.9	61.7	14.8	**90.1**
No (%)	28.4	43.2	16.0	61.7	39.5	53.1	38.3	85.2	9.9

A further area of interest was the participant's perception of the cause of their symptoms. They were asked to tick the cause of their symptoms from a list, selecting as many causes as they believed fit. The table below (table 3.6) demonstrates how the most common beliefs about causes of their CFS were virus and stress. Taking part in too much exercise was the next most common response for cause of symptoms. Eighty-seven percent (87.7%) of the adolescents reported that they regularly took part in exercise before their diagnosis.

Table 3.6: The participant's beliefs about the cause of their CFS (% yes)

	Environment	School	Friends	Virus	Not enough exercise	Stress	Family problems	Too much exercise
%	14.1	19.2	11.5	**56.4**	6.4	**43.6**	6.4	23.1

When asked whether anyone in their family suffered from CFS, 19.2% of the CFS group said they did have a family member with CFS. There was uncertainty amongst the adolescents with CFS regarding recovery. A total of 85.9% reported they did not know how long it would take to recover from CFS.

MINI data; psychiatric diagnoses

Forty-four (51.8%) of the CFS group had an Axis 1 diagnosis. The numbers of participants with Axis 1 diagnoses are shown in table 3.7. The most common co-morbid diagnoses were anxiety disorders and depressive disorder.

Table 3.7: Total number of Axis 1 Psychiatric Diagnoses with the CFS group

Axis 1 Diagnosis	CFS (*N*=85) [% (*N*)]
None	48.2 (41)
Major depressive disorder	**12.6 (15)**
Recurrent major depressive disorder	**10.9 (13)**
Dysthymia current	0.8 (1)
Panic disorder current	5.0 (6)
Panic disorder previous	1.7 (2)
Agoraphobia current	4.2 (5)
Social Phobia current	2.5 (3)
Generalised anxiety disorder current	**12.6 (15)**
Any suicide risk	4.2 (5)
Specific phobia current	1.7 (2)
Separation anxiety current	1.7 (2)
Post-traumatic stress disorder current	0.8 (1)
Obsessive compulsive disorder current	0.8 (1)

Medical co-morbidity

At the time of assessment, thirty seven percent (37%) of adolescents with CFS were also seeing a doctor for other current medical problems (migraines, allergies, joint conditions, anaemia, thyroid problems, fibromyalgia and irritable bowel syndrome). Forty-four (43.8%) percent of the adolescents with CFS had had other medical problems in the past (primarily recurrent tonscilitus, glandular fever and other viruses, but also eczema, headaches, and injuries). Thirty percent (30.9%) of the CFS group had had operations in their childhood. Finally, 55% of the CFS group were currently taking prescribed medication. These were the contraceptive pill, melatonin, amitryptiline, fluoxetine, unspecified meds/anti-depressants, tetralysol antibiotic, ritalin, pain killers,

sleeping tablets, citalopram, omeprazole, hayfever relief, iron tablets and thyroxin. These statistics were much higher than the healthy control group; only 5.1% of them reported that they were currently seeing a doctor, 14.1% had had any medical problems in the past and 12.8% of them were taking any medication at the moment.

All adolescents with asthma were using prescribed medication for their asthma symptoms. In terms of other illnesses in the asthma group, allergic rhinitis ('hayfever') and various other allergies were most common (25 out of 31; 80.6%) and 2 patients also had eczema (6.5%). Corresponding medications (allergy medications such as cetirizine or piriton were used), as well as eczema creams.

School attendance

All 3 groups were asked to report how many full days and half days they attended school on an average week and this was converted into a percentage. The results are presented in table 3.8. As would be expected, there was a significant difference between the groups in terms of time at school. A one-way independent ANOVA revealed that the CFS group missed significantly more time from school than the other two groups. There was no difference between the healthy control and asthma groups. The mean attendance at school in the CFS group was 46.65%.

Table 3.8: School attendance in percentage for each of the 3 groups

	Number	**Mean (%)**	**Std. Dev.**
Chronic Fatigue Syndrome	85	46.65	36.37
Healthy Control	78	100	.00
Asthma	31	99.68	1.80

Wechscler Abbrieviated Scale of Intelligence

The groups were compared to see if there was a difference between groups on overall IQ using a one-way independent ANOVA. There was a significant difference between the groups. Post hoc comparisons using the LSD test indicated that the mean score for the CFS group was significantly lower than the healthy control group as well as the asthma group. The analyses were then repeated for verbal and performance IQ separately. The significant difference remained in the verbal IQ subscales, but not the performance IQ subscales. The results are displayed in table 3.9.

Table 3.9: Adolescent IQ; Means, standard deviations and result of one-way ANOVA

	N	**Mean**	**Std. Dev.**	**Result of one-way ANOVA**
Chronic Fatigue Syndrome	62	100.66	11.490	**Full scale IQ: F(2,166) = 6.202, p = .003*** **Verbal IQ: F(2,167) = 3.351, p = .037*** Performance IQ: F(2,167) = 2.054, p = .131
Healthy Control	78	106.87	12.978	
Asthma	31	108.0	8.064	

Beliefs and behaviours in response to illness

The CFS group scored significantly higher than the asthma group on all 7 subscales of the CBRQ; negative beliefs about engaging in activity, catastrophising beliefs, damage beliefs, embarrassment avoidance (when controlling for scores of depression this finding was no longer significant; F(1,108) = 3.023, p = .085; appendix 9, page 434),

symptom focusing, all or nothing behaviours and avoidance of activity behaviours. See Table 3.10.

Table 3.10: Beliefs and behaviours in response to illness - Clinical groups only (CBRQ); means, standard deviations and results of the independent t-tests

Questionnaire scales	**CFS (N=83)**		**Asthma (N=31)**		**Results of the independent t-tests**
	Mean	**SD**	**Mean**	**SD**	
Negative beliefs about engaging in activity (CBRQ)	14.73	3.61	8.94	4.75	**t(112) = 6.99, p = .000***
Catastrophising (CBRQ)	7.82	3.15	2.90	2.90	**t(111) = 7.55, p = .000***
Damage beliefs (CBRQ)	10.02	3.32	6.61	3.84	**t(112) = 4.68, p = .000***
Embarrassment avoidance (CBRQ)	8.86	4.97	4.81	4.80	**t(111) = 3.91, p = .000***
Symptom focusing (CBRQ)	11.61	5.03	6.84	5.27	**t(111) = 4.44, p = .000***
All or nothing behaviour (CBRQ)	9.17	4.56	3.10	3.30	**t(112) = 6.77, p = .000***
Avoidance of activity behaviour (CBRQ)	14.32	5.30	5.90	4.57	**t(112) = 7.82, p = .000***

A higher score on each CRBQ subscale indicated a greater degree of exhibiting this cognition / behaviour.

Personality Measures

There were no differences between the groups for unhelpful beliefs about experiencing or expressing negative emotions as measured by the BES.

The CFS group scored significantly higher on the doubts about actions subscale of the FMPS. On the parental expectations subscale, the post-hoc tests revealed that the healthy control group scored significantly higher than the CFS group on this subscale, but there were no differences between the asthma group and the CFS group or the asthma group and the healthy controls. There were no differences on any of the other aspects of perfectionism; the other FMPS scales, or self-oriented and socially prescribed

perfectionism (CAPS). According to methods by Stumpf & Parker (2000), perfectionism as measured by the FMPS was then split into healthy (organisation and personal standards) and unhealthy / negative perfectionism (doubts about actions, concern over mistakes, parental expectations and parental criticism). No significant differences between the groups emerged.

There was a significant difference between the groups on the neuroticism subscale of the EPQ. The CFS group scored significantly higher than the healthy controls for neuroticism. There was also a significant difference between the groups on the Extraversion subscale. The CFS group scored significantly lower than both the asthma group and the healthy controls.

There was a significant difference between the groups on scores of social desirability. Post-hoc tests revealed that the CFS group had higher scores than both the asthma group and the healthy controls. Results for all of these factors are shown in table 3.11.

Table 3.11: Personality questionnaires: means, standard deviations and result of one-way ANOVAs for all groups

Questionnaire scales	**CFS (N=83)**		**Asthma (N=31)**		**Healthy Controls (N=78)**		**Results of one-way ANOVAs**
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Neuroticism subscale of EPQ	6.05 [a]	3.09	5.77 [a]	3.06	4.33	3.15	**F(2,189) = 6.55, p = .002***
Extraversion subscale of EPQ	6.37	3.91	8.52 [a]	3.29	8.65 [a]	2.88	**F(2,188) = 10.05, p = .000***
Self-oriented perfectionism subscale of the CAPS	38.64 [a]	4.10	38.29 [a]	5.05	28.51 [a]	4.08	F(2,188) = .09, p = .914
Socially-prescribed subscale of the CAPS	26.42 [a]	6.87	27.42 [a]	6.35	28.41 [a]	6.51	F(2,187) = 1.79, p = .171
Concern over mistakes (FMPS)	18.23 [a]	8.04	18.03 [a]	5.99	18.38 [a]	6.83	F(2,188) = .03, p = .973
Personal standards (FMPS)	20.20 [a]	6.86	18.87 [a]	3.99	20.77 [a]	5.13	F(2,188) = 1.19, p = .306
Parental expectations (FMPS)	10.09 [a]	3.92	11.87 [a]	4.31	13.58	4.41	**F(2,188) = 13.84, p = .000***
Parental criticism (FMPS)	6.41 [a]	2.62	6.90 [a]	2.57	7.49 [a]	3.52	F(2,188) = 2.53, p = .082
Doubts about actions (FMPS)	10.71	3.96	9.29 [a]	3.21	9.31 [a]	3.30	**F(2,188) = 3.58, p = .030***
Organisation (FMPS)	18.92 [a]	5.76	19.23 [a]	5.76	20.23 [a]	5.90	F(2,188) = 1.08, p = .341
Total score on FMPS	65.64 [a]	20.22	64.97 [a]	16.81	69.53 [a]	18.36	F(2,188) = 1.08, p = .343
Healthy perfectionism (FMPS)	39.12	10.99	38.10	6.42	41.00	9.14	F(2,188) = 1.29, p = .279
Unhealthy perfectionism (FMPS)	45.45	14.77	46.10	13.86	48.76	15.14	F(2,188) = 1.06, p = .349
Beliefs about emotions	32.87 [a]	14.26	30.48 [a]	11.37	31.55 [a]	14.51	F(2,188) 0.39, p = .681
Social desirability scale	24.62	8.59	18.35 [a]	7.53	20.94 [a]	8.81	**F(2,188) = 7.29, p = .001***

a Values that have the same superscript are not significantly different from each other.

Higher scores on these scales indicate a greater degree of exhibiting these traits.

Mood / Co-morbidities

The CFS group scored significantly higher than the asthma group and the healthy controls for symptoms of anxiety and depression according to the STAI and CDI respectively. On the CDI, the mean score in the CFS group was above the clinical cut-off of 13 (mean 14.34). There was no significant difference between the groups on social phobia and anxiety as assessed by the SPAI-c and the groups did not meet clinical cut-off for social phobia or anxiety on this measure. Results are displayed in table 3.12.

Table 3.12: Mood questionnaires: means, standard deviations and result of one-way ANOVAs for all groups

Questionnaire scales	**CFS (N=83)**		**Asthma (N=31)**		**Healthy Controls (N=78)**		**Results of one-way ANOVAs**
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Social phobia and anxiety inventory	13.06[a]	9.86	10.93[a]	9.91	10.06[a]	7.42	F(2,176) = 2.21, p = .113
State subscale of the STAI	43.94	11.80	35.90[a]	10.61	34.62[a]	11.44	**F(2,185) = 13.93, p = .000***
Trait subscale of the STAI	46.38	10.75	40.26[a]	11.11	37.49[a]	11.19	**F(2,185) = 13.14, p = .000***
Children's depression inventory	14.34	7.72	7.24[a]	5.38	5.64[a]	5.18	**F(2,187) = 39.11, p = .000***

[a] Values that have the same superscript are not significantly different from each other. Higher scores on these scales indicate a greater degree of exhibiting these traits.

Fatigue and impairment scales

The results indicated significantly worse fatigue, physical functioning and school and social adjustment in the CFS group than either of the other two groups. On the SASA scale, the mean score in the CFS group was 24.42. It has been suggested that scores

over 20 would indicate moderately severe or worse psychopathology (Cella *et al.*, 2011).

The CFS group also had significantly worse quality of life than either of the other two groups, both overall and for all 4 subscales of this measure (PEDS QoL).

On the insomnia sale there was a significant difference between the groups. Post-hoc tests revealed that the CFS group scored significantly higher than both the asthma and healthy control groups. Table 3.13 displays the findings.

Table 3.13: Fatigue and impairment scales: means, standard deviations and result of one-way ANOVA for CFS group, healthy controls and asthma group

Questionnaire scales	**CFS (N=83)**		**Asthma (N=31)**		**Healthy Controls (N=78)**		**Results of one-way ANOVA**
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Chalder Fatigue Questionnaire (binary)	8.21	3.07	1.81[a]	1.72	1.29[a]	1.74	**F(2,189) = 186.98, p = .000***
Chalder fatigue questionnaire (full 33 score)	23.09	6.16	12.0[a]	2.54	10.46[a]	3.76	**F(2,188) = 150.83, p = .000***
School and social adjustment scale	24.42	7.79	2.00[a]	3.587	1.09[a]	3.10	**F(2,189) = 388.43, p = .000***
SF36 physical functioning scale	49.94	25.90	88.39[a]	12.14	90.38[a]	16.99	**F(2,189) = 86.79, p = .000***
Insomnia scale	22.43	9.49	11.81[a]	9.42	8.65[a]	8.80	**F(2,189) = 47.44, p = .000***
Pediatric Quality of Life Scale (overall total)	49.76	14.06	14.62[a]	11.55	17.35[a]	10.26	**F(2,187) = 175.90, p = .000***

[a] Values that have the same superscript are not significantly different from each other.

Maternal report about the child

There was a significant difference between the CFS group and the healthy control group on the overall score of the autism spectrum quotient. The Tukey post-hoc test revealed

that the mothers of the CFS group rated their child significantly higher than the healthy control mothers rated their child and higher than the asthma group, although not significantly (p = .075). Three of the subscales of this measure were significantly different between the groups. Post-hoc tests revealed poorer social skills in the adolescents with CFS than the healthy controls. The attention switching subscale was significantly different between groups. The mothers reported the adolescents with CFS had most difficulty switching their attention; the mothers of the CFS group rated their child significantly higher than the asthma group. Finally, the communication skills subscale was significantly different between the groups, where the CFS group had the lowest on the communication skills, but were only significantly different from the healthy controls not the asthma group.

Table 3.14: Maternal report about the child; means, standard deviations and result of one-way ANOVA for mothers in CFS group, healthy controls and asthma group

Questionnaire scales		**CFS (N=83)**		**Asthma (N=31)**		**Healthy Controls (N=78)**		**Results of one-way ANOVA**
		Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Maternal Report about the child	**Adolescent autism spectrum quotient**	5.25	4.53	3.27 [a]	3.89	23.40 [a]	4.03	**F(2,184) = 4.568, p = .012***

[a] Values that have the same superscript are not significantly different from each other.

Discussion

Main findings

The main aim of this chapter was to conduct a cross-sectional study, investigating factors hypothesised to be associated with CFS in young people. The results will be discussed in turn, beginning with the demographic findings.

Demographic information

There were no significant differences between the groups on age, sex, ethnicity or main carer. This meant that these factors did not need to be controlled for in the above discussed analyses. IQ is discussed separately below.

Although the findings did not reach significance (p = .070), the main carer in the CFS group was more frequently 'mother only' compared to the other groups, with a smaller percentage both parents. This finding may suggest a different family dynamic in the CFS population. The CFS group all met CDC diagnostic criteria for CFS. The adolescents with CFS reported greatest impairment with study and physical exercise. This perhaps highlights the mental and physical impact of the condition. Specific attentional and concentration problems as well as issues with exercise will be addressed experimentally later on this thesis (Chapter 5).

As with previous studies (Marshall *et al.*, 1991; Petrov *et al.*, 2011), the primary symptom of CFS is fatigue, but other important symptoms were unrefreshing sleep, muscle pain and headaches. As was discussed in the literature review (chapter 1), there is some evidence that CFS in young people is a heterogeneous condition. May, Emond & Crawley (2009) undertook a factor analysis of items endorsed on a symptom checklist by young people with CFS and reported three different phenotypes. They labelled these "musculoskeletal" (e.g. muscle pain, joint pain), "migraine" (which included headache, abdominal pain and hypersensitivity to noise, light and touch) and "sore throat" (characterised by sore throats and swollen lymph nodes). The authors reported that worse fatigue, pain and physical function were cross-sectionally associated with musculoskeletal and migraine phenotypes. In this type of study the phenotypes identified will depend on the list of symptoms chosen by the researcher but seemingly,

there is a pattern emerging of key symptoms in adolescents with CFS. Studies in the adult literature (Nisenbaum *et al.*, 2004; Wilson *et al.*, 2001) also support the notion that the presentation of CFS is heterogeneous.

School attendance was significantly worse in the CFS group than either of the other two groups. In this age group, time missed from school can have serious educational and social implications and highlights the importance of engaging these patients into treatment as soon as possible to minimise time missed from school. It is possible that as the young person continues to experience fatigue and disability, they may reduce their daily activities further in an attempt to control the symptoms, which would include missing school or social activities. This puts them at risk of becoming more isolated from their peers and increasingly behind with their school work. This can contribute to the development of further distress, sometimes anxiety or depression, which in turn causes more fatigue and other physical symptoms.

IQ

There was a significant difference between the groups on scores of IQ. The CFS group had a significantly lower IQ than the healthy controls or the asthma group. It must be highlighted that the IQ in the CFS group was not low. It was in fact average (Mean = 100.66). The asthma and healthy control groups IQ were above average. It is possible that there was a bias in the participants in the control groups that resulted in higher IQ as these participants were recruited through 'volunteer sampling' whereby the participants 'self-selected' themselves into the project.

It is also possible that the differences in IQ reflect cognitive impairments in adolescents with CFS (e.g. (Haig-Ferguson *et al.*, 2009)), where the adolescents have problems with memory and attention, which could be associated with intellectual abilities. Adolescents with CFS have not previously been found to have reduced IQ in comparison to healthy controls (e.g. (Carter *et al.*, 1995)). Ideally, these adolescents with CFS would have their IQ reassessed on recovery as it is possible that their IQ was affected by their illness. In this study, all differences remained when controlling for overall IQ. IQ will be controlled for on the experimental tasks (chapter 5) as well to rule out any influence on possible group differences. It cannot be ruled out that the CFS group had lower IQ pre-morbidly (again remembering that their IQ was not low, simply lower than the controls). A previous study found that parents of children with CFS were over-estimating their child's IQ (Godfrey *et al.*, 2009). If a child has an IQ lower than their parents' estimate, this could result in them working hard and struggling to keep up with parental expectations, which could potentially contribute to fatigue symptoms.

Beliefs and behavioural responses to symptoms

As hypothesised, the CFS group scored significantly higher than the asthma group on all 7 subscales of the Cognitive Behavioural Responses Questionnaire. This is the first time these constructs – catastrophising beliefs, damage beliefs, embarrassment avoidance beliefs, symptom focusing, negative beliefs about engaging in activity, all or nothing behaviour, and avoidance of activity behaviours - have been investigated in young people with CFS. These items specifically relate to cognitive behavioural constructs from models of CFS in adults (e.g. (Surarwy *et al.*, 1995)) and adolescents

(Chalder *et al.*, 2002) and it is suggested that they may act as maintaining factors for the condition.

Once triggered (e.g. by infection or stress, with higher levels of both self-reported in the demographics of this chapter), other influences (such as reducing activity due to concern about making symptoms worse) may inadvertently perpetuate the fatigue and other symptoms, leading to substantial disability. In this study, the young people with CFS had significantly more negative beliefs about engaging in activity as well as avoidance of activity behaviours, supporting this aspect of the cognitive behavioural model of CFS in children and adolescents. In adults, fears about the nature of the illness, the meaning of symptoms, the consequences of activity and fear that activity or exercise will make symptoms worse are common (Deale *et al.*, 1998). This current study has identified similar concerns and behaviours in adolescents with CFS (including catastrophizing and damage beliefs).

In an understandable response to such beliefs, the young person may use coping responses that can help control fatigue in the short-term. In the long-term these strategies will inadvertently add to symptom severity and impairment in daily living activities (Chalder *et al.*, 2002). One such proposed maintaining factor, identified in the present study, is excessive rest and avoidance of activity. This can result in reductions in physical conditioning and difficulties tolerating normal activities. There is consistent evidence from a cross-sectional study that young people with CFS tend to favour rest over exercise as a coping strategy (Richards *et al.*, 2005). Prospective evidence is still needed.

It is likely that these unhelpful beliefs about activity may also affect ‘all or nothing behaviour’. In this study, adolescents with CFS had significantly higher scores for all or

nothing behaviours than the asthma group. This behavioural pattern is also known as a "boom and bust" approach. It is characterised by periods of prolonged rest interspersed with bursts of activity. Activity becomes symptom dependent and as time goes on, the symptoms become more and more controlling. This fluctuation in activity levels is addressed in cognitive behavioural therapy (e.g. (Chalder *et al.*, 2002)) with patients encouraged and supported in developing a consistent routine to avoid this 'boom and bust' approach to activity.

Symptom-focusing is described by cognitive behavioural models (e.g. (Surarwy *et al.*, 1995)) as a further potential maintaining factor in addition to the unhelpful beliefs and behaviours surrounding exercise. It is suggested that in an effort to control and reduce symptoms, patients become hyper-vigilant and over-sensitised to bodily symptoms, which may exacerbate unpleasant sensations. The young people with CFS reported significantly higher levels of symptom focusing than the adolescents with asthma as expected. This has been associated with fatigue in adults with CFS (Ray *et al.*, 1993) and in a cross-sectional questionnaire study with adolescents (Gray & Rutter, 2007). Symptom focusing is considered to be a key component in the maintenance of CFS in adulthood (Deale *et al.*, 1998) and the present findings indicate that the same is true in young people with CFS. Experimental techniques and prospective studies are recommended to investigate symptom focusing and the other possible maintaining factors further.

In adults with CFS, Knudsen *et al.* (2011) reported that patients on long-term sickness absence scored higher for embarrassment avoidance cognitions and avoidance of activity behavioural responses. In the present study, group differences on the embarrassment avoidance subscale of the CBRQ was no longer significant when

controlling for depression (p = .085). The fact that depression reduces the effect of these specific beliefs suggests that low mood could be accounting for some of the embarrassment avoidance beliefs, or conversely that the embarrassment and associated avoidance contributes to low mood.

Given the cross-sectional nature of this study, one cannot determine whether these factors are acting to perpetuate the fatigue and disability in adolescents with CFS. Future studies could address whether beliefs and / or behaviours mediate change in fatigue and associated symptoms. Treatment studies could investigate change over time and which factors change first. For instance, do unhelpful beliefs about engaging in activity change first influencing avoidance of activity behaviours, or perhaps the other way around. Cognitive behavioural interventions are based on these constructs and often focus on these assumed perpetuating factors.

Attributions of illness

The most common attribution by the young people with CFS for the onset of their symptoms was a virus. In a proportion, it is possible that the virus may have played an important part in terms of triggering fatigue. A previous study demonstrated a link between an objective measure of a virus and subsequent fatigue (e.g. (Katz *et al.*, 2009)). Longitudinal studies have demonstrated that physical illness attributions for fatigue predict the degree of disability in adults with CFS (e.g. (Sharpe *et al.*, 1992)). Stress was the next most commonly attributed cause of illness in these adolescents with CFS. However, in this study psychological attributions were less rare than in previous studies. Perhaps adolescents with CFS are less wary of psychological explanations than in the past. Or perhaps 'stress' is seen as a factor outside of the self rather than an

internal psychological vulnerability factor. A lot of the young people with CFS as well as their mothers seem open to both psychological and physiological factors when attributing the cause of the CFS. Of course, the interaction between psychosocial factors and physical factors cannot be ignored clinically. There is a consensus that childhood trauma or other life events and chronic stressors might cause long-term impairment in terms of the ability to successfully adapt to stress, for example via disturbances to the HPA axis or autonomic dysregulation, thereby conveying a risk to developing CFS.

Personality factors

As personality traits are generally assumed to be persistent individual characteristics, it is suggested that these factors investigated in the present study (e.g. social desirability, neuroticism and doubts about actions) may be predisposing factors. It is not difficult to speculate that being excessively conscientious or rigid may make it more likely for the individual to become stressed and hence more fatigued in the context of extra challenges such as physical illness or life events. In this study, the CFS group had significantly higher scores of social desirability and neuroticism and lower extraversion scores. This supports the previous literature which suggests that certain personality traits, including excessive conscientiousness, rigidity, fearful behaviour and sensitivity are reported more frequently in adolescents with CFS than healthy controls (Rangel *et al.*, 2005).These qualities may have advantages in some contexts. However, issues may arise if these factors interfere with an appropriate response to stressful situations (e.g. infection or extra school demands) which are commonly associated with the onset of CFS.

Neuroticism is already known to be a factor that predisposes people to develop depression (Teasdale & Dent, 1987). Neuroticism scale items also overlap with depression (e.g. 'does your mood often go up and down'). Neuroticism could be deemed to be a measure of emotional affect or instability. Given this, it is perhaps unsurprising that when controlling for depression in this study, the neuroticism subscale of the EPQ was no longer significantly different between groups. It is possible that the neuroticism is accounted for by higher scores of depressive symptoms in the CFS group.

Cognitive behavioural models of CFS propose that perfectionism leads to increased fatigue and disability through a rigorous attempt to meet high standards (e.g. (Lloyd *et al.*, 2012)). A failure to meet these perfectionist standards leads to increased effort, which subsequently leads to exhaustion and increased levels of fatigue. The adolescents with CFS had significantly higher scores on the doubts about actions subscale of the Frost multidimensional perfectionism scale (FMPS), as was hypothesised. The 'parental expectations' subscale of the same measure was highest in the healthy control group which is counter to predictions. It was hypothesised that the CFS group would score higher on measures of perfectionism. Parental expectations are investigated experimentally in chapter 5. Here, no other subscales were significant, either on the FMPS or the child and adolescent perfectionism scale (CAPS).

A number of cross-sectional studies in adults have reported higher levels of perfectionism in adults with CFS compared to healthy controls e.g. (White & Schweitzer, 2000). This study found patients with CFS to have more 'evaluative concerns', where the doubts about actions subscale was significant. The findings in adults remain inconclusive with some studies reporting no association between higher

scores and CFS (Wood & Wessely, 1999). Deary and Chalder (2010) highlighted different aspects of perfectionism, in adult patients with CFS. They found greater evidence of "unhealthy" rather than "healthy" perfectionism. In the present study, no significant differences between the groups emerged on these subcategories. Moss-Morris, Spence & Hou (2011) reported that perfectionism predicted the onset of new cases of CFS in adults.

Counter to prediction, perfectionism generally as a trait did not differ significantly between the groups. It is possible that the level of perfectionism in the CFS population is largely comparable to the control groups. Perhaps the evidence or lack thereof, suggests that perfectionism is not important in a model of CFS in adolescents. Further studies in both adults and young people would be warranted to fully investigate this characteristic.

A possible reason why certain aspects of perfectionism did not emerge as significant in this study when it is often reported clinically is that since the onset of the condition, perfectionist tendencies may have subsided, given the adolescents' lack of involvement in education and activities. There may also be issues around an awareness of one's own perfectionism at that young age, or some of the participants may be reluctant to acknowledge psychological risk factors. Clearly this needs further investigation before any conclusions can be drawn.

On the beliefs about emotions scale, contrary to the hypothesis, there was not a significant difference between groups. This is also contrary to findings in adults (Rimes & Chalder, 2010). It was theorised that unhelpful beliefs about emotions, or negative thoughts about expressing emotions, would be important in CFS, as a failure to acknowledge emotions is thought to contribute to levels of fatigue. Seemingly in

adolescents this was not the case. It is possible that unhelpful beliefs about expressing emotions did not emerge in the adolescents with CFS because they do not respond to emotions in the same way as adults with CFS. Beliefs about emotions may not be as relevant to this adolescent population as was anticipated. It is also possible that the adolescents were unaware of their own tendencies for expressing emotions and could not quantify their beliefs in order to accurately respond to the questionnaire. This warrants further investigation as this was the first study to investigate possible unhelpful beliefs about emotions in this adolescent population.

As personality traits are generally assumed to be persistent individual characteristics, it is suggested that these factors may be predisposing factors to CFS. Indeed it is not difficult to speculate that having excessive doubts about actions, or being overly neurotic may make it more likely for the individual to become stressed and hence more fatigued in the context of extra challenges such as physical illness or life events. However, due to the cross-sectional nature of this chapter, the possibility of personality alterations occurring as a result of CFS cannot be ruled out. However, there is a lot of research to support the notion that personality shows great continuity from the age of 3 throughout the adolescent years and into adulthood (Caspi, 1998). For example, if a young child was shy and inhibited, they are more likely to be anxious and inhibited when they reach adolescence (Kagan *et al.*, 1994). Recent research using different methodologies suggests that personality can be reliably assessed in adolescence (Westen *et al.*, 2003).

Mood / co-morbidities

Consistent with previous studies (e.g. (Crawley *et al.*, 2009; Walford *et al.*, 1993)), there were significantly higher scores on symptoms of anxiety and depression in the CFS group than the other groups, as measured by the STAI and CDI respectively. This supports the previous literature which showed strong evidence of increased rates of psychiatric co-morbidity in adolescents with CFS compared to healthy or ill control groups (e.g. (Walford *et al.*, 1993)). Depressive disorders and anxiety disorders were the most commonly reported co-morbid problems in the CFS group on the routine psychiatric screening using the MINI. The MINI is a semi-structured interview and this gives added strength to the existing literature rather than self-report questionnaires only. It is possible that disabling fatigue is a risk factor for the development of a psychiatric disorder, but this is all cross-sectional data and the presence of depression may also act to maintain the condition. In adults there is evidence from prospective studies that psychiatric disorders increase the risk of subsequent CFS (e.g. (Wessely *et al.*, 1996)).

Surprisingly, there were not significantly higher scores for social phobia and anxiety as measured by the social phobia and anxiety inventory (SPAI-c). The non-significant finding on the SPAI-c may be partly due to a power issue, as the scores were higher in the CFS group than the other two groups even though this did not reach statistical significance.

A prospective study of young people found that anxiety, depression and conduct disorders at time 1 were associated with increased fatigue and chronic fatigue 4-6 months later (Rimes *et al.*, 2007). It is suggested that psychiatric disorder may be both a predisposing and perpetuating factor for CFS in young people. However more research is needed into this issue.

The emergence of certain psychopathologies during adolescence could be related to typical adolescent maturation changes which occur in concert with psychosocial factors (e.g. school or social stresses). This time period appears to be the central period of risk for the development of mild symptoms of anxiety through to full anxiety disorders (Kessler *et al.,* 2005), depression (Cyranowski *et al.,* 2000) and chronic fatigue and CFS (Chalder *et al.,* 2003; Rimes *et al.,* 2007). Given that anxiety disorders and depression have been found to be associated with chronic fatigue and they occur at a similar stage of development it seems likely that these disorders have some common risk factors. These may include stress (Cohen *et al.,* 1987), parenting style and certain vulnerable personality characteristics.

Given the overlap with psychiatric disorders, management plans should address these problems. Treatment should be tailored to specific personality types, and should address certain individual characteristics such as symptoms of anxiety. Fisher and Crawley (2012) suggest that those with high levels of anxiety require individualised treatments tailored to their different types of anxiety as part of their treatment.

Fatigue and impairment

As predicted the CFS group reported significantly worse fatigue, physical functioning and greater impairment on daily functioning (school and social adjustment). The CFS group also reported significantly worse physical, emotional, social and school functioning than the other two groups as measured by the pediatric quality of life scale (PEDS). These key outcome measures are higher in the CFS population than healthy controls as well another chronic illness group (asthma). CFS is characterised by higher scores of mental and physical fatigue, and is associated with profound disability, so this result is not surprising.

Higher scores on these measures do highlight how debilitating the condition can be. Symptoms are known to vary from person to person, as well as fluctuate from time to time. Clearly though, these symptoms are present and problematic in this condition. It suggests that these factors may be symptoms of CFS specifically rather than chronic illness generally.

Maternal report about the child

The overall score on the autism spectrum questionnaire was significantly higher in the CFS group, with 3 significant scales; poor social skills, poor attention switching and poor communication. These 3 subscales and their items reflect constructs that are often clinically reported to be difficult for adolescents with CFS (Haig-Ferguson *et al.*, 2009). This may predate the CFS, making the child more vulnerable to the condition, perhaps due to finding common situations more stressful due to increased social anxiety and the reported higher levels of neuroticism. Adolescents with CFS may have difficulties with social skills due to being isolated socially if they have not been able to attend school due to their illness. Adolescents with CFS often report problems with attention and it is interesting that this is reflected in the maternal report (attention switching). This was also reported in the Haig-Ferguson et al. (2009) study. In their study, children, parents and teachers alike described problems with focussed attention, sustained attention, recall and stress in the adolescents with CFS. Further, van de Putte *et al.* (2008) found greater distractibility in CFS patients compared to healthy controls on a flanker task.

Limitations of this study

This study was cross-sectional in design. Given this, it is not possible to ascertain the directionality of these associations. Future research would involve prospective research into these constructs. This is described in a subsequent chapter of this thesis (chapter 8, page 296). This will enable further understanding of the factors in terms of directionality.

Chapter summary

Young people with CFS had higher scores than participants with asthma on measures of unhelpful cognitive and behavioural responses to symptoms. These responses provide some evidence for maintaining factors in a cognitive behavioural model of CFS (e.g. negative beliefs about engaging in activity, symptom focusing, and all or nothing behaviours). The beliefs and behaviours about exercise and activity as well as a tendency to symptom focus may act in a cyclical way to maintain the CFS once triggered. These factors need to be a key focus of treatment of CFS in adolescents. Higher scores of neuroticism, doubts about actions, social desirability, as well as anxiety and depression were observed in the adolescents with CFS. These factors are suggested to impact upon a young person's vulnerability to developing CFS. Large, prospective studies are needed (chapter 8, page 296). Experimental designs could help better explain the cognitive, behavioural and emotional coping behaviours in young people with CFS (chapter 5, page 182).

Chapter 4: Clinical characteristics of mothers' of adolescents with CFS

Synopsis

The role parents play in CFS in adolescents is poorly understood. Previous literature has reported both higher levels of maternal distress as well as higher levels of emotional over-involvement in mothers of young people with CFS compared to healthy controls (e.g. (Rangel *et al.*, 2005)). The aim of this study was to examine maternal distress and other psychological variables (including personality, and beliefs about their child's symptoms) in mothers of adolescents diagnosed with CFS, compared to mothers of adolescents with asthma or who were healthy. It is theorised that these maternal factors may be both predisposing and perpetuating factors in adolescent CFS.

Eighty five mothers of adolescents with CFS, 78 mothers of healthy controls and 31 mothers of adolescents with asthma were asked to complete questionnaires to assess these psychological factors.

Compared to mothers of adolescents with asthma, mothers of adolescents with CFS had more negative beliefs about their child engaging in activity and catastrophic beliefs and damage beliefs about their child's symptoms. They also reported more all-or-nothing behaviour and avoidance of activity behaviours in their child.

The mothers of adolescents with CFS reported significantly higher levels of symptoms of depression and anxiety than the mothers in the other 2 groups. Mothers of adolescents with CFS reported a significantly worse quality of life, worse general health and more self-sacrificing behaviours than the mothers in the other two groups. The mothers of adolescents with CFS attributed the cause of their child's CFS most commonly to virus and stress. Finally, the mood/atmosphere at home was significantly

worse in the CFS group, as reported by the mothers on the SCORE40, a family functioning measure. On the family response questionnaire, mothers in the CFS group had significantly higher self-report scores on the sympathetic-empathic, rejecting-hostile and concerns-with-self subscales compared to the other two groups. There were no significant differences between the groups on maternal perfectionism or unhelpful beliefs about emotions.

Although this study is cross-sectional, the results are consistent with the suggestion that maternal factors, particularly maternal distress, may be associated with the predisposition and / or perpetuation of CFS in adolescents. The self-report measure of worse mood in the families of children with CFS supports the suggestion that distress in the family is an important factor in this condition. It also points towards the need to include family factors in a bio-psychosocial model of CFS and to include the family in treatment.

Introduction

It has been suggested that CFS in young people is influenced by functioning within the family (Viner & Christie, 2005). This may involve family stress, close losses, or parental distress. This chapter will investigate clinical characteristics in the mothers that are hypothesised to act as risk factors for CFS in young people.

Parenting a child with Medically Unexplained Symptoms

Ill children need physical and personal care and attention. On a very basic level, a mother may have to stop spending time doing what they were doing (e.g. working) to look after their child. If the child is unwell, they may become worried, they may have to make arrangements for the child to be looked after. It impacts upon their lives in more than an emotional way. Commitments outside may also become increased (e.g. GP visits). One must consider the impact of these experiences and disorders on the children and their families (Eminson, 2007). Further, young people are dependent on their family to make decisions for them. This could be a real burden for mothers. Parents have to learn how to deal with disruption. With Chronic Fatigue Syndrome and other medically unexplained symptoms, there is the added difficulty of managing a child with a poorly understood diagnosis and the inevitable impact this has on family life. There is considerable uncertainty surrounding medically unexplained symptoms and it can be very difficult to manage (Reid *et al.*, 2001).

Maternal beliefs about the child's symptoms

In the previous chapter it was reported that adolescents with CFS have more negative beliefs about symptoms and the consequences of activity than adolescents in the asthma group (other chronic illness). It is likely that the child will partly develop their own beliefs in relation to those of their parents. This may arise from mothers' direct expression of their own beliefs or via the implicit message from mothers' encouraging avoidance and resting behaviours. In adults, avoidance of activity or negative beliefs about activity has been associated with maintaining the condition (e.g. (Sharpe *et al.*, 1992)). In this chapter, it is predicted that mothers of adolescents with CFS will report more negative beliefs about symptoms and the consequences of activity than mothers of adolescents with asthma.

As well as beliefs about symptoms, maternal beliefs about the cause of their child's condition may have a significant influence over the child's cognitive, behavioural and emotional responses to their symptoms. Garralda and Rangel (2005) reported that 72% of parents attributed the cause of their child's CFS to biological factors. It is hypothesised that parents are more likely to attribute the cause of illness to physical causes in this study.

Maternal distress

Five cross-sectional studies (Chalder *et al.*, 2003; Missen *et al.*, 2012; Rangel *et al.*, 2005; Rangel *et al.*, 2000b; van de Putte *et al.*, 2006) have previously investigated the association between maternal distress and fatigue. They each reported more maternal psychiatric symptoms and chronic health problems in the mother of CFS patients when compared to healthy controls, juvenile arthritis and a better CFS outcome group. It is

not known whether the maternal distress is a consequence of CFS in the child or vice versa due to the nature of the studies. Mothers completed the general health questionnaire (GHQ); a measure of distress, in the Rimes *et al.* (2007) study, where a higher GHQ score was associated with fatigue persisting in the child at time 2 (4-6 months later). This suggests that maternal distress may be perpetuating the condition.

The current study aims to investigate maternal distress and CFS in the child further. The GHQ (described in the method section, page 150) is used, with a larger sample than the previous studies. It also uses a new illness control group, asthma. Questionnaire measures of symptoms of depression, anxiety and self-rated quality of life are also used.

Maternal responses to illness

Both theory and research on parenting style (e.g. (Baumrind, 1971, 1991)) are supported by findings that a controlling, authoritarian style of parenting is coupled with higher levels of psychological disorder when compared to a supportive and warm style (e.g. (Darling & Steinberg, 1993; Parker, 1979)). A review of childrearing practices (Rapee, 1997) reported a consistent pattern of rejection and control by parents being related to anxiety and depression in the child, with some of the literature pointing specifically towards rejection being associated with depression and over-protection associated with anxiety. Supportive parenting styles exhibiting emotional warmth on the other hand have been associated with low levels of perfectionistic concerns (Miller-Day & Marks, 2006).

This study will investigate maternal responses to young people with CFS in comparison to maternal responses to children with asthma using the Family Response Questionnaire (FRQ) (Cordingley *et al.*, 2001). This scale was specifically developed for use in

families where there is a child with CFS. It is theorised that findings from this scale may inform future family-based interventions for CFS in adolescents.

Garralda *et al.* (1999) found that adolescents with a history of CFS did not report different levels of parental care and overprotection compared to a healthy control group on the Parental Bonding Instrument (Parker *et al.*, 1979). However, subsequent studies found contradictory results. Based on scores of overprotection, self-sacrificing and pre-occupation with the child, families of children with CFS were characterised by significantly greater emotional over-involvement compared to families of juvenile rheumatoid arthritis or emotional disorders. This was measured by the Camberwell Family Interview (Vaughn & Leff, 1976). In adults with CFS, there is evidence, again from a cross-sectional study, that CFS patients were more likely to report their mothers as over-protective of them (Fisher & Chalder, 2003).

In addition, in this study, the child's own report of parenting will be measured using the EMBU-c ('memories of upbringing' scale). It is hypothesised that the adolescents with CFS will report higher levels of anxious rearing in their mothers as well as higher levels of over-protection than the adolescents in the other groups. This questionnaire was collected at the same point as all of the data reported in chapter 3.

Mothers were also asked to rate their own self-sacrificing behaviour using the self-sacrificing scale of the Young Schema Inventory (Young, 1990). Self-sacrificing behaviour is characterised by sacrificing one's personal interests or well-being for the sake of others or for a cause. Higher levels of self-sacrificial behaviours have been reported in adults with CFS (Hambrook *et al.*, 2011). If mothers of adolescents with CFS are higher on this characteristic, not only may they be modelling this to their child but it could be adding to the mother's own stress levels. Clinical anecdotal evidence

suggests that many mothers of adolescents with CFS give up some or all of their work outside of the home in order to look after the child. Occupational status will be measured as part of a demographic questionnaire.

Maternal emotional processing

Unhelpful beliefs about emotions have been reported in adults with CFS (Rimes & Chalder, 2010). This fits in with cognitive-behavioural models (Surarwy *et al.*, 1995) where it has been suggested that beliefs about the unacceptability of experiencing or showing negative emotions and thoughts can be crucial in the development and perpetuation of clinical characteristics of CFS (Surarwy *et al.*, 1995). Beliefs about emotions in children with CFS were investigated for the first time in the previous chapter. Contrary to expectations, no differences between groups emerged. This maternal questionnaire study investigates the mother's own beliefs about emotions. One reason for this is to see whether children may have learnt such beliefs from their parents. It is suggested that these beliefs are more likely to develop in individuals who have grown up in an environment where the reporting of difficulties or negative feelings was met with a lack of sympathy or punishment (Surarwy *et al.*, 1995). The correlation between the parent and child beliefs about emotions will be measured and reported.

It has been suggested that more negative beliefs about the unacceptability of emotional experience and distress will be associated with greater attempts to suppress or conceal emotions (Surarwy *et al.*, 1995). Therefore it is expected that the mothers in the CFS group will report significantly greater emotional concealment than the other two groups, which will be assessed in the current study using the Affective Style Questionnaire.

Maternal Personality

Personality factors in children often show significant association with those of their parents, which seems to be due to both genetic and environmental influences (e.g. (Harris, 2011)). Maternal perfectionism, neuroticism and extraversion are personality characteristics that will be investigated in the present study. This follows preliminary evidence of higher levels of neuroticism and perfectionism, and lower levels of extraversion in young people with CFS (chapter 3).

Although not previously tested in mothers of adolescents with CFS, higher levels of neuroticism have been found in the mothers of adolescents with chronic abdominal pain (Hotopf *et al.*, 1997). Neuroticism is associated with an increased tendency to experience distress. Maternal neuroticism may contribute to CFS not only via contributing to the child's own neuroticism, but via the mother's own tendency to worry about their child's symptoms and to encourage avoidance behaviours.

Drawing on social learning theory (Bandura, 1977), a 'parent's perfectionism hypothesis' (Stoeber & Childs, 2014) suggests that children and young people may develop perfectionism by 'observing and imitating' their parents' perfectionism. A series of studies report significant correlations between perfectionism in students and their parents' (e.g. (Frost *et al.*, 1991; Vieth & Trull, 1999)). However, these findings do not rule out the possibility of genetic or other influences in this association. The same could be true for the other 'personality' factors.

It is possible that if the mothers' of adolescents with CFS have higher perfectionist tendencies, this may result in young people being more vulnerable to developing the condition in the first place. It may also act to maintain the condition once triggered. This could be by having such high expectations for the adolescent (or family) that the child

strives to achieve something - even when unwell - leading to persistence of fatigue. If the child does not succeed, this could result in avoidance of future attempts because the goals are unrealistic or unattainable. This tendency towards perfectionism, from the mother (and child) may contribute to all or nothing criteria for performance, or all-or-nothing behavioural responses, which are also hypothesised to act to maintain the condition.

Maternal report about the family environment

Family functioning style is a way of describing how a family deals with life events and how they develop and work together. Researchers have reported that people use different coping styles in response to different life events and the resources available to them (Trivette *et al.*, 1990). It is possible that if there are higher levels of distress or more stress through life events in the family, this may impact upon family functioning and the way people deal with situations.

No previous study investigating CFS in adolescents has investigated the role of family functioning. This study will use a family functioning scale (SCORE40) (Stratton *et al.*, 2010) to identify the characteristics of the family as described by the subscales; mood/atmosphere, flexibility/adaptability, communication, danger/hostility and roles/rules/individuation. These are all aspects of interpersonal relationships among family members. Given that previous studies have observed higher levels of distress in the adolescents with CFS as well as parental scores, it is hypothesised that there will be higher scores on this measure in the CFS group. This will suggest worse family functioning.

Hypotheses

Maternal beliefs about the child's symptoms

The mothers of the CFS group will report more negative beliefs about their child engaging in activity and more catastrophic beliefs and damage beliefs about symptoms than the mothers in the asthma group.

The mothers in the CFS group will also report more all or nothing behaviour and avoidance behaviours in their child than the asthma group.

It is hypothesised that the mothers in the CFS group will attribute the cause of their child's illness mainly to physical causes.

Maternal distress

Mothers of adolescents with CFS will self-report more symptoms of fatigue, anxiety, depression, and distress and worse quality of life than mothers of healthy adolescents or adolescents with asthma.

Maternal responses to illness

The mothers in the CFS group will exhibit more difficulty in coping with their child's illness than the mothers in the asthma group. This will include more sympathetic-empathic responses towards the child, active engagement and rejecting-hostile responses towards the illness and higher concern with self (how the illness affects their own life).

It is hypothesised that the mothers in the CFS group will report more self-sacrificing behaviours than the mothers in the other two groups.

It is hypothesised that the adolescents with CFS will report higher levels of anxious rearing in their mothers as well as higher levels of over-protection than the adolescents in the other groups.

Maternal emotional processing

The mothers of the CFS group will have more unhelpful beliefs about the acceptability of experiencing or expressing negative emotions (BES).

The maternal CFS group will have significantly higher scores of concealing and lower scores of adjustment and tolerating affect on the subscales of the Affective Styles Questionnaire.

Maternal personality

The mothers of young people with CFS will self-report higher levels of neuroticism, and perfectionism than mothers of healthy adolescents or adolescents with asthma.

Maternal report about the family environment

The mothers in the CFS group will report worse family functioning and a more negative view of the family and its environment than the mothers in the other two groups.

Method

Design

This was a cross-sectional, questionnaire study. The design included 3 participant groups; mothers of adolescents with CFS, mothers of adolescents with asthma and healthy control mothers. Eighty five mothers were in the CFS group, 31 mothers in the asthma group and 78 mothers in the healthy control group.

The CFS group were recruited sequentially from a specialist CFS clinic with the family being given an information sheet to return. The asthma and healthy control groups replied to a letter about the study (as described further in participants section in chapter 2, page 73) and opted to take part in the study thereafter.

Procedure

All mothers in the study were asked to complete a series of questionnaires (appendix 10, page 436). These were completed at the first time point, after consent had been given (the same time as when the child completed their questionnaires). All questionnaires were returned before the experimental tasks were completed with the adolescents.

Demographic data and clinical characteristics of the mothers'

The mothers were asked to report their ethnicity, occupational status, occupational status of their partner and marital status.

There was minimal missing data, but unfortunately, there were some mothers who did not complete the questionnaires. One mother (asthma) did not speak English, 1 mother (CFS) had severe mental health issues and could not complete the questionnaires, 1 mother had passed away (healthy control) and 1 mother (healthy control) did not live with, or have any contact with the child.

Questionnaire measures

The questionnaires used in this study are all well-validated for use with adults; further information is provided below.

Maternal beliefs about the child's symptoms

Cognitive-Behavioural Responses Questionnaire (CBRQ) (Moss-Morris & Chalder, 2003)

This is the same measure that was completed by the child (see chapter 3), but this was reworded for mothers, to assess maternal beliefs about the child's symptoms. Mothers were asked to rate how much they agreed or disagreed with a series of statements asking about their child's current symptoms. For example "I am afraid my son will make his symptoms worse if he exercises". Mothers were also asked to rate avoidance and all-or-nothing behavioural responses in their child. The Cronbach's alpha for the subscales were as follows; negative beliefs about engaging in activity .802, catastrophizing .809, damage beliefs .771, all or nothing behaviour .873 and avoidance of activity behaviours .863.

Maternal beliefs about the cause of their child's CFS

Mothers of adolescents with CFS were asked to complete a questionnaire to report their beliefs about the possible cause of their child's CFS. They were asked to tick the cause of their child's symptoms from a list, selecting as many causes as they believed fit. The options were; environment, school, friends, not enough exercise, stress, family problems, virus and too much exercise.

Maternal distress

Chalder Fatigue Questionnaire (Chalder et al., 1993)

This is a self-rated measure of the severity of fatigue (Chalder *et al.*, 1993). The mothers completed the scale described in full in chapter 3 (appendix 10, page 436) with regard to their own fatigue. The Cronbach's alpha for this scale was .911.

Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983)

The Hospital Anxiety and Depression Scale was selected to help identify symptoms of depression and anxiety in the mothers of the groups. This is a 14-item measure of anxiety (7 items) and depression (7 items). Mothers were asked to rate a series of statements relevant to either anxiety or depression on a four-point (0-3) response category so the possible scores ranged from 0 to 21 for anxiety and 0 to 21 for depression. Higher scores indicated greater levels of anxiety and depression. There is no single, generally accepted, cut-off score for the HADS. However, the authors recommend that for both anxiety and depression raw scores of between 8 and 10 identify 'mild' cases, scores between 11 and 15 identify 'moderate' cases and scores of 16 or above identify 'severe' cases (Zigmond & Snaith, 1983). Missen *et al.* (2012) used the HADS in mothers of adolescents with CFS and reported 41% scored above the cut-off for anxiety and 13% for low mood / depression. The Cronbach's alpha for this study was .857. For the anxiety subscale, the Cronbach's alpha was .790, and for the depression subscale it was .707.

General Health Questionnaire (GHQ) (Goldberg, 1972)

The GHQ-12 was used as a measure of current maternal mental health. Often used as a screening inventory (Fryers *et al.*, 2004) to identify those with probable mental health problems, it is known to have excellent reliability and validity (Goldberg *et al.*, 1997). A score of 1 to 10 indicates 'low psychological distress', 11-12 is 'typical', 13-15 is 'more than typical', 16-20 shows 'evidence of psychological distress' and a score of over 20 indicates 'severe distress' (Goldberg *et al.*, 1997). The scale focuses on two major areas; the inability to carry out normal functions and the appearance of new and distressing experiences. The questionnaire asks whether the participant has experienced a particular symptom or behaviour recently. Each item is rated on a 4-point scale (0, 1, 2 or 3), with a maximum total score of 36. The Cronbach's alpha in this study was .893.

World Health Organisation WHO-5 (Well-being index, 1998 version; World Health Organisation)

The WHO-5 well-being index is a self-report rating scale of 5 items, developed to investigate the concept of subjective quality of life. The five items cover positive mood (good spirits, relaxation), vitality (being active and waking up fresh and rested) and general interests (being interested in things) (Bech, 1998, 2001). Mothers were asked to indicate for each of the five statements which is closest to how they have been feeling over the last two weeks (higher numbers mean better well-being; 0 = not present, 5 = constantly present). The raw score is calculated by totalling the five answers. The raw score ranges from 0 to 25, 0 represents worst possible and 25 represents best possible quality of life. A score below 13 indicates poor well-being and is an indication for testing for depression under ICD-10 (WHO-5). It is a patient friendly measure of well-

being with good psychometric properties (de Wit *et al.*, 2007). The Cronbach's alpha for this scale in this study was .879.

Maternal responses to illness

Family Response Questionnaire (FRQ) (Cordingley *et al.*, 2001)

The FRQ is a 25 item measure which assesses the responses of family members to people with CFS. It assesses the ways of coping with the problems of a person's illness, particularly over the last 3 months. Mothers of adolescents with CFS and asthma were asked to complete the scale given they are a part of a family with a child with a chronic illness. The scale is made up of 4 response scales; sympathetic-empathic (trying to imagine what the patient feels like, making positive support statements), active engagement (doing things for the patient, protecting the patient), rejecting-hostile (disbelieving the patient's complaints or minimising them), and concern with self (concerned with effect of patient's illness on her own life). Measures of test-retest reliability were high (Cordingley et al., 2001). The scale is scored using the following formula (e.g. for the sympathetic-empathic scale): Score = 10 [(∑ items 1, 2, 8, 10, 11 and17) - 7] /7. It is a 5-point likert scale from 0 not at all, to 4 very often. In this study, the Cronbach's alpha was .888. For the individual subscales, the Cronbach's alphas were sympathetic engagement .807, active engagement .709, rejecting hostile .764 and concern with self .638.

Young's Self-Sacrificing Inventory (SQ) (Young, 1990)

Maternal self-sacrificing beliefs and behaviours were measured using the Self-Sacrificing subscale of the Schema Questionnaire (SQ (Young, 1990)). Items for the SQ were generated by its author and other practicing therapists based upon clinical experience with different constellations of beliefs or 'schemas'. Each item is rated using a 6-point scale (1 = completely untrue of me, 2 = mostly untrue of me, 3 = slightly more true than untrue, 4 = moderately true of me, 5 = mostly true of me, 6 = describes me perfectly). The self-sacrificing subscale comprises 17 items to examine exaggerated expectations of duty and responsibility to others. It describes individuals who are most comfortable doing things for others and who feel guilty when they focus any attention on themselves. The total score ranges from 0 – 102, with a higher score indicating more self-sacrificing behaviours. The Cronbach's alpha in this study was .881.

EMBU-c; a Swedish acronym for 'my memories of upbringing' (Gerlsma et al., 1991)

Adolescents were asked to complete this scale. They rated for each parent separately and the final score is separate for mother and father. The questionnaire was completed at the experimental task session rather than being completed with the other questionnaires at home, given the sensitive nature of the questionnaire and to ensure truthful answers.

The Dutch adolescent 81 item version of the EMBU was used as the source for the item pool for young children (Gerlsma *et al.,* 1991). The adolescent version subsequently used fewer items (40 items) and was translated into English. This was the measure used in the current study. There is a column for mother and a column for father. The answer categories are 'no, never', 'yes, but seldom', 'yes, often' and 'yes, most of the time'. It

is a four-point, forced-choice scale with 4 subscales: over-protectiveness, emotional warmth, rejection and anxious rearing. The Cronbach's alpha in the current study was .762. For the subscales, the Cronbach's alphas were .666 for overprotectiveness, .919 for emotional warmth, .841 for rejection and .868 for anxious rearing.

Maternal Emotional Processing

Beliefs about Emotions Scale (BES) (Rimes & Chalder, 2010)

Mothers were asked to complete the BES to assess beliefs about the unacceptability of experiencing or expressing negative emotions. This is the same 12 item scale described in chapter 3 (appendix 10, page 436). Mothers completed this scale in relation to their own beliefs about expressing emotions. The Cronbach's alpha for this scale was .914.

Affective Style Questionnaire (ASQ) (Hofmann & Kashdan, 2010)

This is a 20 item self-report measure of affective style using a 5-point likert rating scale. The ASQ gives total scores for 3 main categories of emotion regulation; adjustment (7 items; the general ability to manage, adjust and work with emotions as needed) concealing (8 items; habitual attempts to conceal or suppress affect), and tolerating affect (5 items; an accepting and tolerant attitude toward emotions). It has been shown to be both a reliable and valid measure of affective style in a healthy student population in the USA (Hofmann & Kashdan, 2010). Higher scores on the adjustment and tolerating affect subscales and lower scores on the concealing subscale indicate positive emotion regulation. In this study, the Cronbach's alpha was .796 for the overall scale and for the subscales respectively, concealing .781, adjusting .731, and tolerating .666.

Maternal Personality

Eysenck Personality Questionnaire (EPQ-R Short-form; (Eysenck et al., 1985))

Mothers were asked to complete the EPQ (described in chapter 3) with their own personality being subjectively measured. The EPQ is a self-report questionnaire based on Eysenck's theory of personality. The EPQ measures two personality tendencies; neuroticism and extraversion. The neuroticism scale (N scale) measures the degree to which the individual is predisposed to experience negative affect. An example of a question on the N scale is "do you often feel lonely?" or "are you a worrier?" The extraversion scale (E scale) assesses the degree to which individuals are sociable, active and impulsive. An example of this subscale includes "are you a talkative person?" or "do you enjoy meeting new people?" The Cronbach's alpha for the subscales were .868 for extraversion and .800 for neuroticism.

Frost Multi-dimensional Perfectionism Scale (FMPS) (Frost et al., 1990)

The FMPS is a 35-item multidimensional scale to measure perfectionism and details of this scale were discussed in chapter 3. The mothers were asked to report their own beliefs and behaviours on this widely used scale in personality and clinical research. On this scale, the Cronbach's alpha for the individual subscales was as follows; concern over mistakes .902, personal standards .800, parental expectations .791, parental criticism .867, doubts about actions .804 and organisation .881.

Maternal report about the family functioning

Describing your Family (SCORE40) (Stratton et al., 2010)

The SCORE40 is a measure of family functioning (Stratton *et al.*, 2010). The SCORE40 has 40 items about how the family functions, rated on a 6 point likert scale, where 1 = extremely well, 2 = very well, 3 = well, 4 = a bit, 5 = not well and 6 = not at all. Mothers were asked to report about how they see their family at the moment; their view on their family. The original 40 item scale has good psychometric properties (Stratton *et al.*, 2010) and has 5 key constructs; mood/atmosphere, flexibility/adaptability, communication, danger/hostility and roles/rules/individuation. The likert scale scores positive ratings at 1 and negative at 6, with the scoring of negative items reversed. A low final score is a positive evaluation of the family. Scores range from 0 to a maximum 240.

Measures designed to provide information on family relationships and functioning are not in routine clinical use but can be very informative in reflecting family environments. The mothers were rating their relationship with the current household / family i.e. their own child and spouse where relevant. In this study, the Cronbach's alpha was .596 for the overall scale. For the individual scales, the Cronbach's alphas were .791 for mood/atmosphere, .711 for flexibility and adaptability, .723 for communication, .315 for damage / hostility and .366 for rules roles and individuation. The alphas for the final two subscales are not very reliable, and this will need to be considered when interpreting findings.

Data preparation and Statistical Analysis

All scales were scored using Syntax for SPSS. Pro-rating was described in chapter 2. Chi-squared analyses were used to investigate whether the groups differed significantly on the categorical (demographic) variables. The two control groups (asthma and healthy controls) were combined for the demographic analyses as this is in line with the predictions. One would not expect the two control groups to differ. Also, for some analyses the cell sizes were too small for Pearson Chi-squared otherwise.

Tests for normality were conducted. According to the Q-Q plots and histograms, the data was normally distributed and met assumptions for parametric analyses. One-way ANOVAs were used to compare scores across the 3 groups and independent t-tests were used for the two measures completed by the two chronic illness groups only. Levene's test for homogeneity of variance was conducted. Where this was significant, the Welch statistic and where necessary the Games-Howell (GH) post-hoc test was used. Otherwise, Tukey post-hoc test was used to investigate the differences between the groups. Correlations between child and parent questionnaires were conducted using Pearson's r.

Results

Demographics

Sample characteristics are reported for the mothers of each group in the tables below.

Ethnicity

A Pearson's chi-squared test was used to test for differences among the groups for ethnicity. Ethnicity status was combined into 'white' or 'other' for the purpose of group

comparisons as the cell sizes were otherwise too small. There was a significant difference between the ethnicity of the mothers, with the CFS group having a higher percentage of white mothers than the controls; χ^2 (1,189) = 4.074, P = .044*. Table 4.1 shows the breakdown of all ethnicities for separate groups as well as healthy control and asthma combined and other ethnicity (not white) combined.

Table 4.1: Ethnicity of mother for all 3 participant groups

	White (%)	Black (%)	Asian (%)	Other (%)	All non-white combined (%)
CFS	94.0	2.4	0.0	3.6	6.0
Asthma	76.7	13.3	3.3	6.7	23.3
Healthy Controls	88.0	6.7	4.0	1.3	12.0
Asthma and healthy controls combined	84.8	8.6	3.8	2.8	15.2

Occupational Status

A chi-squared test was used to test for differences in occupational status between the mothers in the 3 groups. All categories indicating 'not employed' were combined so that chi-squared assumptions were met and comparisons could be made. Analyses revealed that there was a significant difference in occupational status, χ^2 (1,189) = 4.522, p = .033*. There were significantly fewer mothers in the CFS group who were employed compared to the controls. Table 4.2 shows the breakdown of different occupational status groups for the mothers. The final column is the combination of the previous totals not in the employed percentage.

Table 4.2: Occupational status of mothers for all 3 participant groups

	Employed (%)	Unemployed (%)	Student (%)	Housewife (%)	Disability Allowance (%)	Other (%)	Combined other (%)*
CFS	61.9	4.8	3.6	19.0	6.0	4.8	38.1
Asthma	86.7	0.0	0.0	6.7	0.0	6.7	13.3
Healthy Controls	72.0	0.0	5.3	16.0	0.0	6.7	28.0
Asthma and healthy controls	76.2	0.0	3.8	13.3	0.0	6.7	23.8

Marital Status

A chi-squared test revealed there was not a significant difference between the 3 groups on marital status when combining all non-married categories due to cell size, χ^2 (1, 188) = 2.210, p = .137. Table 4.3 shows the marital status percentages for each of the 3 groups.

Table 4.3: Marital status of mothers for all 3 participant groups

	Married (%)	Single (%)	Divorced (%)	Co-habiting (%)	Widow (%)	Partner, not living together (%)	Other (%)	Other combined (%)
CFS	61.9	6.0	14.3	11.9	0.0	2.4	3.6	38.1
Asthma	76.7	10.0	10.0	0.0	0.0	3.3	0.0	23.3
Healthy Controls	70.3	9.5	2.7	10.8	1.4	4.1	1.4	29.7
Asthma and healthy controls combined	72.1	9.6	4.8	7.7	0.9	3.8	0.9	27.9

Maternal beliefs about the child's symptoms

The mothers of the adolescents with CFS had significantly higher scores than the asthma group on their own negative beliefs about their child engaging in activity, catastrophising beliefs and damage beliefs about their child's symptoms. The mothers in the CFS group also rated that their child engaged in significantly more all or nothing behaviours and avoidance of activity behaviours than the asthma group. All subscales of the cognitive-behavioural responses questionnaire were significantly different between the two groups. The results are shown in table 4.4.

Table 4.4: Maternal beliefs about the child's symptoms

	Construct	CFS (N=84)		Asthma (N=30)		**Result**
		Mean	S.D	Mean	S.D	
Chronic conditions only (maternal report of child's beliefs and behaviours)	Negative beliefs about engaging in activity (CBRQ)	12.68	3.81	8.10	3.28	**t(112) = 5.978, p = .000***
	Catastrophising (CBRQ)	6.87	2.78	1.80	3.91	**t(112) = 9.076, p = .000***
	Damage (CBRQ)	10.18	3.02	6.63	3.91	**t(112) = 5.098, p = .000***
	All or nothing behaviour (CBRQ)	7.14	4.37	2.70	2.12	**t(112) = 5.342, p = .000***
	Avoidance / resting behaviour (CBRQ)	13.16	5.42	3.77	1.92	**t(112) = 13.645, p = .000***

Attributions for illness

The mothers were asked to tick the cause of their child's symptoms from a list, selecting as many causes as they believed fit. Table 4.5 demonstrates how the most common beliefs about causes of their child's CFS were virus and stress.

Table 4.5: Mothers' beliefs about the cause of the child's CFS

	Environment	School	Friends	Not enough exercise	**Stress**	Family problems	**Virus**	Too much exercise
% Yes	21.4	17.9	11.9	8.3	**56.0**	11.9	**67.9**	32.1

Maternal fatigue and distress

There was a significant difference between groups on fatigue (CFQ), as shown in table 4.6. The Games-Howell (GH) post-hoc tests revealed the CFS group was significantly higher than the healthy control group, but no significant difference emerged between the CFS group and asthma controls (p=.055).

There was a significant difference between the groups on HADS-anxiety. The post-hoc comparisons (GH) revealed the CFS group was higher than both the asthma controls and the healthy controls. Thirty two mothers of adolescents with CFS (38.1%), 4 mothers of adolescents with asthma (13.3%) and 22 mothers of healthy controls (29%) scored 8 or higher (cut-off) on the HADS-anxiety subscale.

There was a significant difference between the groups on scores of HADS-depression. The post-hoc tests revealed significantly higher scores for depression in the mothers of the CFS group compared to both the asthma controls and the healthy controls. Seventeen mothers of adolescents with CFS (20%), 0 mothers of adolescents with asthma and 1 mother of healthy controls (0.01%) scored 8 or higher (cut-off) on the HADS-depression subscale.

There was a significant difference between the groups on maternal distress as measured by the GHQ. Using post-hoc comparisons, the Tukey test revealed the CFS group had the highest scores, followed by asthma participants and healthy controls had the lowest

scores; with a significant difference between the CFS group and the asthma controls as well as the healthy controls. The higher score indicates worse distress.

There was a significant group difference on quality of life. Post-hoc tests (GH) revealed that mothers of adolescents with CFS had lower scores on the WHO-5 than asthma as well as healthy controls. A score under 13 is the criteria for testing for clinical depression and the mean score for the mothers in the CFS group was 13.21, almost meeting the clinical cut-off. Table 4.6 presents all of these findings.

Maternal responses

Groups were compared on scores of self-sacrificing beliefs and behaviours using the one-way ANOVA, and there was a significant difference between the groups. Post hoc tests revealed a significant difference between the CFS group and both of the other two groups where the highest scores were in the CFS group.

The CFS group had significantly higher scores than the asthma group on the sympathetic-empathic scale of the FRQ, significantly higher scores than the asthma group on the rejecting-hostile scale of the FRQ and significantly higher scores on the concerns-with-self scale of the FRQ. The CFS group did not differ significantly to the asthma group on the active engagement scale of the FRQ.

For the child rating of parenting style (EMBU-c), the only significant subscale was for rejection. Here, the CFS group reported significantly less rejection behaviours from their parents than the control groups reported. Table 4.6 displays the findings for all maternal responses to illness measured.

Maternal Emotional Processing

There were no differences between the groups for beliefs about emotions.

There was a significant difference between the groups on affective style, on the concealing subscale, where the CFS group scored highest, indicating negative emotion regulation; $F(2,188) = 3.22$, $p = .042$*. Here, there was a significant difference between the CFS group and the asthma group, but not between the CFS and healthy control groups or the asthma and healthy control mothers. Neither of the other 2 subscales were different between groups. Table 4.6 displays the findings for maternal emotional processing.

Maternal Personality

Significant group differences were identified on the neuroticism subscale of the EPQ. The mothers in the CFS group significantly differed only from the mothers of adolescents with asthma, not the healthy controls with higher scores of neuroticism in the CFS mothers. There was not a significant difference between the groups on extraversion. When comparing the groups on the scores of perfectionism, there were no differences between the groups on any of the subscales. Table 4.6 presents the analyses for maternal personality measures.

Maternal report about the family environment

There were no significant differences between the groups on the overall total of the family functioning questionnaire (SCORE40). However, there was a significant difference on one of the subscales, the mood/atmosphere subscale. The post-hoc tests

revealed that the mothers of the CFS group reported worst mood/atmosphere in the family home; they scored significantly higher than the asthma group as well as the healthy control group. Table 4.6 shows these analyses.

Table 4.6: Clinical questionnaire data for mothers; means, standard deviations and results of the one-way ANOVAs and independent t-tests

		CFS (n=84)		Asthma (N=30)		Healthy controls (N=76)		Results
Category	Questionnaire/Construct	Mean	SD	Mean	SD	Mean	SD	
Maternal distress	Chalder fatigue questionnaire	3.23	4.41	1.60[a]	2.72	1.8[a]	2.58	**F(2,187) = 4.160, P = .017***
	World Health Organisation 5 (WHO-5)	13.21	4.82	17.37[a]	2.75	17.5[a]	4.72	**F(2,187) = 14.435, p = .000***
	Hospital anxiety and depression inventory – anxiety	7.37	4.39	5.86[a]	2.23	5.93[a]	3.44	**F(2,183) = 3.435, p = .034***
	Hospital anxiety and depression inventory – depression	4.60	3.66	2.38[a]	1.40	3.13[a]	2.35	**F(2,183) = 8.348, p = .000***
	General health questionnaire	13.25	5.06	10.69[a]	4.06	11.37[a]	5.08	**F(2,186) = 4.308, p = .015***
Maternal responses	Active engagement (FRQ)	6.31[a]	5.93	4.22[a]	6.28	###	###	t(106) = 1.559, p = .122
	Sympathetic-empathic (FRQ)	23.21	6.76	14.21	5.26	###	###	**t(106) = 6.302, p = .000***
	Rejecting-hostile (FRQ)	15.61	6.15	10.31	5.16	###	###	**t(106) = 4.025, p = .000***
	Concern with self (FRQ)	12.47	5.46	8.52	5.01	###	###	**t(106) = 3.323, p = .001***
	Self-sacrificing subscale of the YSI	70.00	11.20	59.73[a]	11.10	64.82[a]	14.35	**F(2,187) = 8.284, p = .000***
	Overprotectiveness (EMBU-c) – child report	24.29[a]	5.02	25.17[a]	4.04	23.66[a]	4.26	F(2,152) = 1.16, p = .316
	Emotional warmth (EMBU-c) – child report	33.83[a]	5.66	32.66[a]	6.73	33.94[a]	6.06	F(2,153) = .50, p = .609
	Rejection (higher score indicates more rejection) (EMBU-c) – child report	12.68	3.00	15.17[a]	4.06	15.34[a]	4.90	**F(2,154) = 7.46, p = .001***
	Anxious rearing (EMBU-c) – child report	21.53[a]	5.77	24.59[a]	7.42	22.88[a]	6.58	F(2,151) = 2.20, p = .200

Maternal emotional processing	Beliefs about emotions scale	28.42 [a]	14.32	26.90 [a]	7.50	28.36 [a]	14.52	F(2,186) = .148, p = .862
	Affective style questionnaire	65.92 [a]	8.83	63.53 [a]	8.44	66.93 [a]	9.84	F(2,185) = 1.466, p = .233
Maternal personality	Neuroticism (EPQ)	5.05 [a]	3.20	3.38	2.60	4.37 [a]	2.60	**F(2,185) = 3.350, p = .037***
	Extraversion (EPQ)	7.54 [a]	3.72	8.28 [a]	2.96	7.89 [a]	3.53	F(2,183) = .509, p = .602
	Frost multidimensional perfectionism scale	87.86 [a]	19.58	83.93 [a]	17.83	91.68 [a]	20.42	F(2,182) = 1.757, p = .175
Maternal report about the family environment	SCORE 40 – describing the family	83.77 [a]	20.46	77.23 [a]	16.25	82.70 [a]	18.02	F(2,186) = 1.347, p = .262

[a] Values that have the same superscript are not significantly different from each other

Correlations between child and parent questionnaires

There were some significant correlations for those scales completed by both child and mother. Correlations were investigated separately within each of the three groups investigated (see table 4.7). For the CFS group, there were significant correlations between the adolescents with CFS and their mothers on scores of anxiety and each of the subscales of the Cognitive Behavioural Responses to Symptoms Questionnaire.

Adolescents with asthma and their mothers were significantly correlated on scores of personal standards, parental expectations and overall perfectionism, and four of the five subscales of the Cognitive Behavioural Responses to Symptoms Questionnaire.

The healthy controls were significantly correlated with their mothers on concerns over mistakes, parental criticism, doubts about actions, total perfectionism and scores of depression as well as quality of life.

Table 4.7: Correlations between child and parent questionnaire measures (Pearson r) - Significant findings are in bold for ease of reading

		CFS	Asthma	Healthy Control
Self-rating scales	CFQ	.214, p = .054	-.082, p = .665	.131, p = .259
	BES	.092, p = .411	.270, p = .156	.211, p = .069
	Concern over mistakes	.057, p = .615	.159, p = .409	**.347, p = .003***
	Personal standards	.169, p = .132	**.406, p = .029***	.199, p = .093
	Parental expectations	.192, p = .086	**.470, p = .010***	.221, p = .062
	Parental criticism	.112, p = .321	.128, p = .508	**.251, p = .033***
	Doubts about actions	.186, p = .097	.075, p = .699	**.376, p = .001***
	Organisation	.172, p = .124	.051, p = .794	.079, p = .510
	Total Perfectionism	.147, p = .189	**.436, p = .018***	**.389, p = .001***
	Neuroticism	.188, p = .091	-.214, p = .266	.008, p = .944
	Extraversion	.138, p = .222	-.187, p = .331	.046, p = .697
	Children's depression inventory & Parent's General health questionnaire	.108, p = .342	-.248, p = .194	.131, p = .260
	Children's depression inventory & Parent's depression (HADS)	.147, p = .197	-.286, p = .133	**.228, p = .049***
	State anxiety and parent anxiety (HADS)	.124, p = .285	-.265, p = .165	.028, p = .813
	Trait anxiety and parent anxiety (HADS)	**.285, p = .012***	-.017, p = .930	.132, p = .257
	Negative beliefs about engaging in activity	**.431, p = .000***	**.412, p = .024***	###

	Catastrophising	**.257, p = .021***	**.692, p = .000***	###
	Damage	**.295, p = .007***	**.474, p = .008***	###

Discussion

Summary of main findings

The main aim of this cross-sectional study was to explore some of the maternal factors that may be predisposing and / or perpetuating CFS in adolescents. The findings identify an excess of CFS-like problems in mothers of young people with CFS, and more maternal distress than in the other two groups. Mothers of adolescents with CFS reported a significantly worse quality of life, worse maternal mental health (GHQ), more symptoms of depression and anxiety, and significantly more self-sacrificing behaviours than the mothers in the other two groups.

Compared to mothers of adolescents with asthma, mothers of adolescents with CFS reported more negative beliefs about their child engaging in activity and more catastrophic beliefs and damage beliefs (believing symptoms are a sign of damage) about their child's symptoms. These mothers also reported significantly more avoidance of activity and more all or nothing behaviours in their child with CFS. Mothers of adolescents with CFS attributed the cause of their child's illness most commonly to either a virus or stress (similarly to the adolescents themselves), seemingly open to the influence of both kind of factors. The mood and atmosphere at home was significantly worse in the CFS group, as reported by the mothers on the SCORE40, a family functioning measure. This was the only significant subscale of this measure of functioning.

Contrary to the hypotheses, there was not a significant difference between the groups on any of the perfectionism subscales, or the beliefs about emotions scale measuring

unhelpful beliefs about the experiencing or expression of negative emotions. It is possible that these factors are not relevant in this study population – indeed the CFS mothers are largely similar to the healthy population mothers on this measure.

There was a significant difference between the groups for ethnicity as well as the percentage of mothers in employment. There was a significantly higher percentage of white mothers in the CFS group than the combined control group (asthma and healthy controls). A significantly lower percentage of mothers in the CFS group were in employment.

Discussion of findings

Maternal beliefs about the child's symptoms

Compared to mothers of adolescents with asthma, mothers of adolescents with CFS reported more negative beliefs about their child engaging in activity, more catastrophic beliefs and damage beliefs about their child's symptoms. Damage beliefs denote a tendency to believe that symptoms are an indication of damage to the body.

The cognitive behavioural models of CFS suggest the negative beliefs may act to maintain CFS (e.g. (Surarwy *et al.*, 1995; Wessely *et al.*, 1989)) by encouraging rest and avoidance behaviours. Prolonged rest and inactivity are seen as central in sustaining the cycle of symptoms and disability. Added to the responses by the adolescents themselves, these findings suggest that the treatment approaches that challenge unhelpful cognitive and behavioural responses to symptoms may be important in improving the overall management of fatigue and disability in CFS. All subscales

completed by the child and their mother correlated. It is possible that beliefs in the mother may be related to the formation of beliefs in the child, although this cross-sectional data cannot test this hypothesis. Thus, identifying psychological issues in mothers when developing a child's treatment may facilitate the success of treatment overall. This was true of maternal depressive symptoms and treatment adherence to asthma therapy (Bartlett *et al.*, 2004).

Maternal fatigue and distress

A greater proportion of the CFS mothers reported a previous history of CFS. This increased rate of CFS-like illness in parents of adolescents with CFS is consistent with the previous findings of Bell *et al.* (1991) and Rangel *et al.* (2005). The nature of this relationship between maternal and child fatigue is unclear, i.e. whether it reflects shared genetic or environmental vulnerability factors or whether there is social learning.

There were significantly higher scores in the CFS group on the GHQ (maternal mental distress) and the HADS (anxiety and depression subscales) as well as the WHO-5. This suggests that the health and well-being of the mothers' of adolescents with CFS is generally worse than those in the other two groups. However, the scores of anxiety and depression did not reach any case-ness in the mothers. These findings which highlight a significant level of maternal distress in this population are in line with the five cross-sectional studies (Chalder *et al.*, 2003; Missen *et al.*, 2012; Rangel *et al.*, 2005; Rangel *et al.*, 2000b; van de Putte *et al.*, 2006). These all reported more maternal psychiatric symptoms and chronic health problems in the mother of CFS patients when compared to healthy controls, juvenile arthritis and a better CFS outcome group. It remains unclear

whether the elevated maternal distress is due to the illness of the child and the understandable worry this causes, whether the worse general health pre-exists, or whether both interact in a mutually unhelpful manner. This area warrants further investigation, as previous research has reported that those children who have parents with a psychiatric condition have problems at school and socially as well as increased somatic complaints (Downey & Coyne, 1990).

Maternal responses

When considering possible differences between groups in this chapter, one must be mindful of how the results may be evidence of a maternal reaction to the impairment in their child. Quite simply, ill children need physical and personal care and attention. On a very basic level, a mother may have to stop spending time doing what she was doing (e.g. cleaning) to look after the child – this will naturally appear as self-sacrificing.

The mothers of adolescents with CFS reported greater levels of self-sacrificing behaviours than the mothers in the other two groups. This study is the first to use a measure specifically assessing self-sacrificing behaviour. The findings are in line with the previous literature looking at similar constructs (Garralda & Rangel, 2005). Garralda and Rangel (2005) reported higher scores on a 6-point emotional over-involvement questionnaire (Vaughn & Leff, 1976) measuring over-protection, self-sacrificing behaviours and pre-occupation with the child, in families of children with CFS compared to families of juvenile rheumatoid arthritis or emotional disorders. Together they suggest greater emotional over-involvement from these mothers (Garralda & Rangel, 2005; Rangel *et al.*, 2005).

A significantly lower percentage of mothers in the CFS group were in employment and this may be an example of self-sacrificing behaviour or over-protection. Clinical anecdotal reports indicate that many of the CFS mothers choose to stop working in order to look after the ill child at home, but this issue requires further research. Return to work for the mother could be an important stage in the child's recovery. Anecdotally, this has been reported as a difficult transition for the mother and child (personal communication)(Chalder, 2012). If the mother has given up work due to the child's illness, it could have a negative impact on her own quality of life and self-esteem and perhaps even their attitude towards their child. Ultimately, it could lead the child to feel guilty, or it may contribute to the child feeling fearful about the severity of their condition. Clearly, this is a complex issue that requires further investigation.

It could be argued that over-protection is a natural response to a chronically ill child, or may be in response to characteristics already shown in the child. However, it is also possible that parental responses may be acting inadvertently to perpetuate the fatigue and / or disability in adolescents with CFS. For example, in their understandable efforts to aid recovery, parents may be doing too much for their child in contrast to encouraging the young person to build up their activity levels. The latter would facilitate confidence in coping with different situations. The illness burden of CFS on the child and their family is very different and indeed can be difficult to manage. This cannot go unrecognised.

Compared to the mothers in the asthma group, the mothers of the CFS group scored significantly higher on the concerns-about-self subscale (of the FRQ). This showed greater concern about the effect the illness may have on her life. Further, the rejecting-

hostile subscale was significantly higher in the mothers of the CFS group, which quantifies an attempt to minimise the symptom complaints of the ill family member. Finally, the sympathetic-empathic responses in the CFS group were higher than the mothers in the asthma group. This could possibly partly reflect the perceived severity of the condition. The mothers of the adolescents with asthma may have fewer concerns about the child's illness despite this being potentially life-threatening for some children. It does highlight a certain pre-occupation with the illness in the CFS group, which isn't necessarily beneficial to the child's recovery. Taken together, the findings of higher scores of rejecting behaviours in addition to higher scores of empathic behaviours do not satisfactorily fit into the previous model of CFS in adolescents (Chalder *et al.*, 2003). It is possible this pattern reflects a real battle for mothers of adolescents with CFS to know how best to deal with this debilitating condition. Sometimes empathy and concern may be considered helpful, other times rejection of the symptoms may be best for the patient. It perhaps highlights the sudden onset of the condition and parents having to learn how to manage the condition and understand it as it constantly evolves.

It is possible that the high level of distress in the mothers of the adolescents with CFS reduces their capacity to respond in the most helpful ways. It is suggested that CBT targeting parenting techniques or addressing general parental (dis)stress may be effective in reducing child distress.

Only one subscale of the EMBU-c was significantly different between groups. This is surprising as one may have expected higher levels of anxious rearing, particularly given the evidence of higher levels of distress in mothers of adolescents with CFS here and in previous literature (e.g. (Chalder *et al.*, 2003)). However, it must be remembered that

this measure is taken from the child's perspective. This supports the message that for parenting, the 3 groups are largely similar. The adolescents with CFS reported significantly less rejection from their parents than the adolescents in the other two groups. It is possible that the parents of adolescents with CFS were paying more attention to their child and their symptoms than the parents in the other two groups. This increased attention may act to maintain symptom-reporting or preoccupation.

Maternal emotional processing

The mothers of adolescents with CFS were found to have significantly higher scores for concealing emotions than mothers of the control groups. This strategy for emotional expression, not letting others see what they're feeling may be counter-productive for the mothers, for example it may reduce their ability to elicit social support. There is evidence that emotional concealment can be a maladaptive emotion control strategy (e.g. (Hayes *et al.*, 1999)). This may be important for the child, as they may learn these approaches to emotion regulation from their families. If there is a family context of emotional concealment, the mother may be less likely to be aware of distress in the child and may interpret physical symptoms as signs of physical illness rather than considering stress as a possible explanation.

Unhelpful beliefs about emotions have been reported in adults with CFS (Rimes & Chalder, 2010). It has been suggested that beliefs about the unacceptability of experiencing or showing negative emotions and thoughts can be crucial in the development and perpetuation of clinical characteristics of CFS (Surarwy *et al.*, 1995). It is suggested that these beliefs are more likely to develop in individuals who have

grown up in an environment where the reporting of difficulties or negative feelings was met with a lack of sympathy or punishment (Surarwy *et al.*, 1995). It was therefore warranted to investigate such beliefs in the mothers of the CFS population. Contrary to expectations, no differences between the 3 maternal groups emerged. Emotional processing and emotional expression in both young people with CFS and their mothers requires further investigation.

Maternal Personality

There was a significant difference between the groups on the neuroticism subscale (EPQ). The mothers in the CFS group had the highest levels of neuroticism across the groups. It is important to consider the possible overlap between measures, particularly neuroticism scores and psychological distress (in this study, Pearson's R=.540, p .000*). The link between neuroticism and distress is well established. For example neuroticism is associated with increased subsequent risk for a range of psychological disorders. The mechanisms underlying this link have received considerable attention (e.g. (Bolger, 1990; Bolger & Schilling, 1991; McCrae & Costa, 1986)). Some authors argue that the measures are distinct, with neuroticism representing a stable personality trait, whereas psychological distress represents a present state (Rodgers, 1990). However, others argue that neuroticism as a tendency to experience distress may show continuity over time (Bolger, 1990).

Neuroticism in the mother may affect the child in a number of different ways, which could be examined in future research. However, it is important to acknowledge that there will be an interaction with the personality of the child. If a child is more prone to

anxiety, they may not adapt as well to extra demands in their life such as exams or difficulties at home. This will likely cause extra stress for the mother.

Contrary to expectations, there were no differences between the groups on any of the subscales of perfectionism. This was surprising given previous findings (Fry & Martin, 1996; Garralda & Rangel, 2001; Godfrey *et al.*, 2009) that there is a tendency for adolescents with CFS and their parents to have unrealistically high expectations of what the child can achieve. It was theorised that these high standards may point towards perfectionist standards. In the previous chapter (chapter 3), higher levels of doubts about actions were found in the adolescents with CFS, but these were not mirrored in the mothers. Let's recognise that in this maternal population the mothers of adolescents with CFS are largely comparable to the control groups for scores of perfectionism and that perhaps this variable is not relevant in a model of adolescent CFS. It is possible that the mothers under-reported their own perfectionism due to a lack of awareness or concerns about possible suggestions that their expectations for their child were too high.

Maternal report of family functioning

On this measure of family functioning, there was only one significant subscale. All other subscales suggested that the CFS families were largely functioning in the same way as the control group families as per the maternal report.

The mothers in the CFS group reported significantly worse mood in the family than the other two groups on this measure. This is consistent with the hypothesis that distress in the family is a prominent feature in this condition. Given the cross-sectional nature of

this study, it is impossible to disentangle cause and effect. The prospective study (chapter 8) will investigate the association further. The results in the current study suggest that it is important to include the family in treatment. Chalder *et al.* (2010) found that initially after a course of family-focused CBT, school attendance and fatigue improved more in the CFS group than in the group of adolescents receiving psycho-education. The authors showed that improvements after CBT were maintained 5 months after treatment (Chalder *et al.*, 2010). Seemingly, working with the whole family is beneficial in the child's recovery status, but it is not known the mechanism by which this occurs.

Correlations between mother and child rated scales

There were some significant correlations across the groups for those scales completed by both child and mother (appendix 11, page 466). Notably, negative beliefs about activity, and catastrophic beliefs about symptoms were significantly correlated between mother and child in both chronic illness groups. Obviously any causal relationship cannot be ascertained but it seems reasonable to suggest that parental modelling and influence may play a role (e.g. self-efficacy (Bandura *et al.*, 1996)). It is likely that unhelpful beliefs in the mother are getting passed on to the child. This important finding requires further research.

There was a significant correlation between the adolescents with CFS and their mothers on scores of anxiety. Again, the nature of this relationship cannot be determined but is likely to be a combination of genetic and environmental factors (e.g. (Bogels & Brechman-Toussaint, 2006)).

Adolescents in the asthma and healthy control groups and their mothers had significant correlations with regard to overall perfectionism on some of the subscales. This correlation was not apparent in the CFS group which is intriguing. It has been suggested that participants with CFS may downplay psychological characteristics due to their strong illness attributions and it is unclear whether this could be a factor contributing to this current lack of association.

Clinical implications

Although firm conclusions cannot be drawn from this cross-sectional data, this study has highlighted that mothers may play a crucial role in the development and / or perpetuation of fatigue and associated symptoms in adolescents with CFS. Treatment will need to explore whether there are any issues in the family that are preventing recovery in the child. Findings of negative and catastrophic beliefs about symptoms and activity in the mother of the young person with CFS suggest that cognitive and behavioural factors need to be addressed with the young person and also the parents. Although this has not been not directly evaluated through mediational analysis for CBT in children with CFS, CBT is assumed to work by changing unhelpful cognitive and behavioural responses to symptoms. Treatment sessions may need to address any factors that may be preventing the child from making changes in their behaviour. Distress and fatigue in mothers could be addressed during family focused CBT but mothers could also be encouraged to seek help from adult services so that their own needs can be addressed.

Strengths and Limitations

A strength of the study was that it included two control groups; mothers of adolescents with asthma and mothers of healthy controls. One limitation is that there was a small chronic conditions sample. However, the study was sufficiently powered to address the research questions (see chapter 2, page 81).

All adolescents were recruited from tertiary CFS units and the results may not be applicable to milder cases or those seen in primary care. This study only reports the clinical characteristics and personality traits of mothers. This is not to detract from the significant influence fathers may also play in the development and perpetuation of the condition in adolescents with CFS. Future studies should report data from fathers.

The number of comparisons made between the groups raises the possibility that some of the statistical significances found could have been due to type 1 errors. Caution should be taken when interpreting the findings. Bonferoni correction was used on all analyses to help address this issue.

Chapter summary

This study reports the important new finding that mothers of adolescents with CFS reported more personal negative beliefs about activity and more catastrophic beliefs about symptoms than the mothers in the asthma group. Consistent with previous studies, higher levels of symptoms of anxiety and depression were found in mothers of adolescents with CFS. Other characteristics of the mothers with CFS included greater neuroticism, self-sacrificing behaviours, and a tendency to conceal emotions.

There is now a better clinical picture of the mothers in the CFS group than before and indeed the family environment. The mothers of adolescents with CFS also respond to illness in a different, perhaps less helpful way, than the mothers in the asthma group. This may be due to their heightened levels of distress and worse reported mood and atmosphere at home.

Future research should involve prospective research into these constructs. The possible prospective association with maternal distress and fatigue is addressed in chapter 8. This will enable further understanding of the factors in terms of directionality. Taken together the findings from this study indicate distinctive features in maternal mental health and family characteristics in childhood CFS. A family approach to assessment and management may be the answer (Chalder *et al.*, 2002).

Chapter 5: An experimental investigation of possible maintaining factors in CFS in adolescents

Synopsis

Experimental tasks were used to test hypothesised maintaining factors in CFS in adolescents. These were derived from cognitive behavioural approaches. The potential maintaining factors under investigation were symptom focusing, expectations of performance, negative performance evaluation, misattribution of symptoms of stress and parental expectations. The performance tasks were attention, exercise and social presentation tasks, none of which had previously been tested in adolescents with CFS.

It was hypothesised that adolescents with CFS, randomly allocated to an experimental task inducing symptom focusing would report greater levels of fatigue and other symptoms than those randomly allocated to a distraction task. It was also hypothesised that adolescents with CFS and their parents would have lower expectations of their performance than the other two groups, particularly on the exercise task. Due to the hypothesised negative perfectionism in the adolescents with CFS, it was predicted that the discrepancy between their self-evaluation of performance and objective performance measures would be larger in the CFS group than the other two groups. It was hypothesised that the CFS group would be more likely to attribute symptoms of physiological dysregulation (stress) to their illness than the asthma group and would be less likely to attribute the symptoms to stress.

Results indicated that compared to distraction, symptom focusing increased physical fatigue in all three groups. The CFS participants showed an increase in mental fatigue and pain after both symptom focusing or distraction conditions, whereas the asthma group showed an increase in mental fatigue and healthy participants showed no increase in mental fatigue or pain. The adolescents with CFS and their parents had lower expectations of performance on the experimental tasks than the other two groups, particularly on the exercise task. The adolescents with CFS rated their post-task performance on all performance tasks as worse than the control groups but this was in line with their poorer objective performance (time taken). The CFS group were more likely to attribute cognitive symptoms of stress to their illness rather than the stress of the task in comparison to the adolescents with asthma.

In conclusion, symptom focusing, lower pre-performance expectations, lower post-performance self-evaluation, misattributions of symptoms as well as lower parental expectations of performance are all factors that may act to maintain CFS in adolescents. These factors are explained in the context of cognitive behavioural models of CFS.

Introduction

The aim of this study was to investigate hypothesised maintaining factors in adolescent CFS derived from cognitive behavioural theory, using an experimental design. To date, experimental studies in adolescents with CFS have rarely been conducted. This chapter will begin with a brief overview of hypothesised maintaining factors in CFS. It then describes the existing evidence so far, for the factors investigated in this study, linking them to the current study and hypotheses.

Maintaining factors for CFS proposed in cognitive behavioural models

Wessely *et al.* (1989) suggested that although fatigue may often have been initially triggered by an infection, other factors may then act to maintain the condition. Wessely et al. proposed that the individual starts to reduce their activity levels in an understandable attempt to feel less fatigued, but in fact their exercise tolerance worsens and hence fatigue increases when they try to do more. Catastrophic interpretations of symptoms and beliefs such as 'there must be something seriously wrong with me' and 'if I continue with this activity I will get so exhausted I will end up bedbound', contribute to activity reduction and avoidance behaviours. They suggest that the individual ends up in a vicious cycle of unhelpful cognitions and behaviours including symptom focusing, activity reduction, exercise intolerance, fatigue and disability. This has led to cognitive behavioural interventions addressing such factors (e.g. (Chalder *et al.*, 2010)). As previously outlined, Surarwy *et al.* (1995) built on this initial model, developing a more cognitive-based theory which captures these important maintaining factors as well as other cognitive factors including high personal standards and self-

expectations. In this study, some of these proposed maintaining factors are investigated experimentally. The factors to be investigated are symptom focusing, pre-performance expectations and anxiety, post-performance self-evaluation, misattribution of symptoms and lower parental expectations of performance.

Cognitive behavioural models in adolescents (Chalder *et al.*, 2002) purported that these same factors interact in adolescents to prevent recovery. Cognitive behavioural therapy (CBT) in adolescents with CFS is derived from such understanding as well as clinical observations. CBT typically involves planned activity and rest and a graded increase in activity, addressing unhelpful beliefs and recognises the importance of involving the family in the approach (e.g. (Chalder *et al.*, 2002; Lloyd *et al.*, 2012)).

Symptom focusing

Symptom focusing may act as a maintaining factor in CFS by a) increasing the likelihood of noticing changes in bodily sensations and intensifying the symptom experience, both of which may then increase the likelihood of catastrophic misinterpretation and b) contributing to difficulties by focusing on other internal and external stimuli, i.e. concentration and distractability problems (Surarwy *et al.*, 1995). A focus on the illness may prevent the patient from tackling difficulties such as psychological or social issues. Cognitive behavioural approaches to depressive rumination in health anxiety also suggest that symptom-focused processing can result in an increase in symptom experience (e.g. (Nolen-Hoeksema & Davis, 1999; Salkovskis & Warwick, 1986)). Earlier in the thesis (chapter 3), it was reported that the CFS group

focused on their symptoms significantly more than the other chronic illness group (asthma), as measured by the cognitive-behavioural responses questionnaire (CBRQ). One could argue that symptom focusing in the asthma group was lower as they are more used to being ill (given the extended duration of their chronic illness), so they focus on the illness less. However, it is also possible that the changes in bodily sensations are greater in the CFS group than the asthma group and this intensifies the symptom experience and encourages symptom focusing. Using the illness perceptions questionnaire (IPQ (Weinman *et al.*, 1996); IPQ-R (Moss-Morris *et al.*, 2002)), Gray and Rutter (2007) investigated symptom focusing in adolescents with CFS. They reported that a greater self-reported focus on symptoms was associated with poorer quality of life. However the direction of causality could not be ascertained from this cross-sectional study.

In the field of depression, there has been much research investigating the impact of focusing on one's symptoms. It has been suggested that the way in which people respond to symptoms of depression will impact the severity and duration of these symptoms (Response Style Theory; (Nolen-Hoeksema, 1991)). Nolen-Hoeksema (1991) defined 'depressive rumination' as the process of "focusing passively and repetitively on one's symptoms of distress and the meaning of those symptoms without taking action to correct the problems one identifies" (Nolen-Hoeksema, 1998). For example "I just can't concentrate" and worrying about the meanings and consequences of the distress; "will I ever get over this?" (Lyubomirsky *et al.*, 1998; Nolen-Hoeksema, 1991). There is considerable evidence that focusing on the causes, meanings and consequences of one's depressive symptoms can intensify or extend the depressive

symptoms, compared to distraction or other forms of self-focused attention (Lyubomirsky & Tkach, 2004; Morrow & Nolen-Hoeksema, 1990; Nolen-Hoeksema & Morrow, 1993). In the current study, the impact of focusing on the causes, meanings and consequences of one's symptoms will be investigated in the context of symptoms of fatigue and associated symptoms.

The aim of this current study was to investigate whether participants who were randomly assigned to an analytical 'symptom-focusing' condition, thinking about the causes, meanings and consequences of their symptoms, would subsequently report greater fatigue and pain than participants asked to focus on distracting items. This paradigm, although widely used to investigate symptom-focused processing in depression in rumination research (e.g. (Lyubomirsky & Tkach, 2004)), has not previously been used in CFS.

Pre-performance expectations and anxiety

Pre-performance expectations

Surarwy *et al.* (1995) reported that adults with CFS in their clinic tended to have high standards for performance, personal conduct and were highly conscientious. There is an assumption that the failure to meet these high self-expectations would indicate failure. Surawy et al. suggest that these high standards for performance can make the patients with CFS vulnerable when faced with demands they cannot meet. A failure to meet expectations leads to increased effort and adds to exhaustion and increased levels of fatigue. A repeated experience of not achieving goals will reinforce negative beliefs that

they are suffering an illness that they cannot overcome. This may cause further distress and avoidance. It may also lead to lower expectations of performance if the individual feels they cannot achieve things to the level they once could.

Inaccurate expectations and unrealistic perceptions were reported with regards to fatigue (Garralda & Rangel, 2001) and activity levels (Fry & Martin, 1996) in adolescents with CFS. Both adolescents with CFS and their parents were found to significantly underestimate the adolescents' current activity levels and had higher expectations of their post-CFS activity levels than was realistic for children of that age (Fry & Martin, 1996). The subjective rating (as measured by visual analogue scales) of activity was significantly lower in the CFS group than the healthy control group, but the actual activity level measured over three days with an activity monitor was comparable across groups (Fry & Martin, 1996). Similarly, Garralda and Rangel (2001) found that adolescents with CFS had unrealistic views of normative fatigue levels as measured by a visual analogue scale.

In the current study, expectations for performance on an attention task, an exercise task and a social performance task will be measured using visual analogue scales. One key reason for investigating expectations surrounding these tasks is that none of these types of tasks have been used before in adolescent CFS.

Prior to the onset of CFS, cognitive behavioural models suggest that adolescents with CFS put themselves under a lot of pressure. After developing the condition they are likely to downgrade their expectations because they attribute performance difficulties to having CFS. It is expected that the adolescents with CFS will have lower expectations of their performance and greater expected difficulty before the performance tasks than

the other two groups. Expectations of performance in the CFS group on the exercise task are predicted to be particularly low. This is because cognitive behavioural models suggest they have developed unhelpful beliefs about the consequences of exercise (Surarwy *et al.*, 1995). If they expect that the exercise is going to make them worse, they may avoid it and may subsequently expect less from future performances (as well as increased difficulty).

Anxiety

High standards and clinical perfectionism may represent vulnerability in situations where control or perceived ability to achieve the high standards is threatened, contributing to anxiety of a situation or task. Perfectionism as a trait is included in cognitive behavioural models of CFS. It is theorised that patients with CFS may hold rigid perfectionist attitudes (Surarwy *et al.*, 1995). Adolescents with CFS in the cross-sectional questionnaire study (chapter 3) were found to have significantly higher scores for doubts about actions than adolescents with asthma or healthy controls. This is one element of clinical perfectionism. It is suggested that people with clinical perfectionism react to failure to meet their standards with self-criticism (Shafran *et al.*, 2002). It is then that negative aspects of perfectionism, (e.g. doubts about actions) may become problematic resulting in fatigue and associated worries which act to maintain the CFS.

Perfectionism in the context of high expectations may contribute to the development of the condition but, later, individuals may lower those expectations due to the fatigue (CFS) and through continued self-criticism due to poorer performance. The key feature

of clinical perfectionism is how high standards are pursued despite significant negative consequences when they are not achieved. The cognitive behavioural model suggests that perfectionism highlights a fear of failure which may develop as a result of such high standards. This may lead to avoidance of activity and an inability to achieve goals (Shafran *et al.*, 2002). The emphasis needs to be on clinical (negative) perfectionism as healthy perfectionism is considered positive and 'normal'. Combined with clinical perfectionism, higher levels of neuroticism may relate to pre-performance anxiety as well as post-performance negative self-evaluation (which is discussed below), whereby more worries about task performance relates to lower expectations about performance.

Post-performance self-evaluations

In addition to the aspects of perfectionism discussed above, cognitive behavioural models also suggest that clinical perfectionism is associated with a critical style of post-performance self-evaluation (e.g. (Shafran *et al.*, 2002)). People are theorised to self-evaluate repeatedly and also in a strict manner. It does not only account for evaluating whether or not they achieved a goal, but also a self-evaluation of their pursuit of the goal (Shafran *et al.*, 2002). It is possible that those who have clinical perfectionism will be self-critical and evaluate their performance in a negative way; noticing their failures in favour of successes (e.g. (Antony & Swinson, 1998)).

It is theorised in this study that due in part to negative perfectionism in adolescents with CFS, there will be a larger discrepancy between self-evaluations and objective performance ratings in the CFS group than the other two groups. Actual performance in adolescents with CFS may be reduced due to the symptoms of fatigue (e.g. slower

performance). The key focus is the discrepancy between perceived and actual performance. Slower performance may also be related to perfectionism in the child. It is predicted that adolescents with CFS will rate their performance more negatively in relation to objective performance, compared to the other two groups. Actual performance on the different tasks (attention, social performance and exercise) will be reported, but the key hypotheses are the discrepancies.

Attributions of symptoms of stress

Wessely *et al.* (1989) proposed that the misattribution of symptoms to illness leads to negative beliefs about exercise. This misattribution may also lead to an avoidance of exercise which may exacerbate the symptoms and lead to de-conditioning (described in chapter 1). Surarwy *et al.* (1995) suggested that reasons for misattribution of symptoms to illness in people with CFS includes a premorbid tendency to believe that there is a physical basis to the illness whilst searching for an explanation for their symptoms. Surawy suggests that this misattribution reduces 'the social blame and loss of self-esteem' that may be experienced otherwise in terms of a failure to perform an activity. Misattribution of symptoms can modify the symptom pattern experienced by the patient. It has been suggested in cognitive behavioural models of CFS in adults that the tendency to make somatic attributions for their condition is due to beliefs about negative emotions being unacceptable and a sign of weakness (Surarwy *et al.*, 1995). In adults with CFS, there is evidence that beliefs about the unacceptability of experiencing or expressing negative emotions are reported to a greater extent in people with CFS than healthy individuals (Rimes & Chalder, 2010) but this thesis was the first to investigate

beliefs about emotions in adolescents with CFS. It found no significant differences between the groups using the beliefs about emotions scale (BES) (Rimes & Chalder, 2010).

Cross-sectional research has consistently reported (6 studies, a mixture of qualitative and quantitative, discussed in detail in chapter 1) that adolescents with CFS (and their families) attribute the cause of their CFS to a physical / biological cause, often rejecting a psychological explanation (e.g. (Garralda & Rangel, 2001)). These studies used a mixture of questionnaires or semi-structured interviews with small groups of adolescents with CFS. This is not necessarily surprising given that in many cases the excessive fatigue began in the context of a virus, but individuals and their families may be overlooking other factors that made the young person vulnerable for fatigue becoming a chronic problem. However, no studies have investigated the way in which adolescents with CFS attribute symptoms of stress within a laboratory setting. Individuals with CFS may fail to recognise the cause of symptoms associated with physiological dysregulation, particularly if they are used to suppressing or hiding their emotions. It was predicted that the CFS group would be more likely to attribute symptoms of physiological dysregulation (stress) caused by the social performance task to their illness than the asthma group and less likely to attribute the symptoms to stress.

Parental expectations

The role of parents in adolescent CFS is also considered to be important. It is thought that illness in the child may be maintained by beliefs and behaviours of the parents. The parental expectations or beliefs may influence the child's beliefs and behaviours,

contributing to fatigue. Fry & Martin (1996) reported that parents of adolescents with CFS had lower expectations of their child's current activity levels, compared to healthy control parents. These lower expectations could result in reduced activity in the child if less is expected of them. This reduced activity could contribute to negative beliefs about engaging in activity for fear of making symptoms worse. Godfrey *et al.* (2009) reported that although adolescents with CFS and healthy controls had similar IQs (no significant differences), parents in the CFS group over-estimated their child's actual IQ in comparison to healthy controls. It is possible that if parents think their child's IQ is higher than it is, the adolescent with CFS may be put under more pressure. In turn, the adolescent tries harder to achieve goals and becomes exhausted. Parents and adolescents alike then believe that the CFS is preventing the child from performing and subsequent expectations about performance reduce. As with the individual's own expectations discussed earlier, if parental goals are not in line with what the individual may realistically achieve or want to achieve and these expectations are expressed to the child, the result may be avoidance of future attempts. This would consequently lower future performance or indeed expectations thereof. In the present study, parents were asked to rate how well they expected their child to do on attention, exercise and social performance tasks, as well as how difficult they would find them. The prediction was that parental expectations would be lower in the CFS group, because of their child's disabilities.

Hypotheses

1) Does symptom focusing increase symptoms of fatigue?

It is predicted that the adolescents with CFS randomly allocated to an experimental task inducing symptom-focusing will report greater levels of fatigue and other symptoms compared to adolescents with CFS randomly allocated to a distraction task.

In contrast, it is hypothesised that the control groups' level of fatigue and other symptoms will not be significantly affected by the condition to which they are randomised.

2) Pre-performance expectations and anxiety

It is hypothesised that adolescents with CFS will be more anxious, have lower expectations of their performance and greater expected difficulty, before the attention, social performance and exercise tasks than the other two groups. It is predicted that these group differences will be particularly low for the exercise task.

3) Post-performance self-evaluation

Due to hypothesised negative perfectionism and higher levels of neuroticism in the adolescents with CFS, it is predicted that the discrepancy between their self-evaluation of performance and objective ratings will be larger in the CFS group than the other two groups; their self-ratings will be more negative relative to objective ratings.

4) Attributions of symptoms of stress

It is hypothesised that the CFS group will be more likely to attribute symptoms of physiological dysregulation (stress) caused by the social performance task to their illness than the asthma group and will be less likely to attribute the symptoms to stress.

5) Parental expectations

It is hypothesised that parental expectations will be significantly lower in the CFS group compared to the control groups because they view their child as particularly disabled by the CFS.

Methodology

Overall procedure

Participants were given general information about what would happen during the session and the opportunity to ask questions before consenting to take part. Adolescents with CFS were seen at the CFS unit and participants with asthma were seen at their GP surgery or the CFS unit. Adolescents in the healthy control group were given the option of being seen at their school or the CFS unit. More details were reported in the Methodology chapter (chapter 2). Tasks were undertaken in quiet rooms, in which the session was undisturbed for the whole task procedure. It was a one-off task session that lasted approximately 2 hours, with a short 10 minute break during the session (after 3 tasks). Full details and verbatim instructions for the experimental procedure are outlined in appendix 12 (page 468). Table 5.1 outlines the standardised procedure.

Table 5.1: The standardised procedure of the experimental task session

Overall discussion of the session and opportunity to ask questions
Baseline cortisol
Baseline visual analogue scales (VAS) assessing current fatigue and associated symptoms
Instructions for Letter Cancellation task
Pre-task VAS for the attention task
Attention task completion – 2 trials
Post-task VAS for the Letter Cancellation Task
Instructions for the Symptom Focusing vs. Distraction Task
Pre-task VAS for the Symptom Focusing vs. Distraction Task
Symptom Focusing vs. Distraction Task completion – 8 minutes
Post-task VAS for the Symptom Focusing vs. Distraction Task
Wechsler Abbreviated Scale of Intelligence (as reported in Chapter 3 with other demographics)
BREAK – 10 minutes
Connect to physiological recording device
5 minute recording of baseline heart rate and skin conductance response
Baseline2 cortisol
Instructions to the Social Performance Task
Pre-task VAS and other questionnaires for the Social Performance Task
-1 minute cortisol
Social Performance Task completion – 3 minute speech
Post-task VAS for the Social Performance Task
+10 minute cortisol
Recovery section on physiological recording device +20 minute cortisol +30 minute cortisol
Instructions to Exercise Task
Removal of physiological recording device

Pre-task VAS for the Exercise Task
Exercise Task completion – 2 trials
Post-task VAS for the Exercise Task (and Borg Scale)
Debrief

Participants

Sixty two adolescents, who fulfilled the Oxford criteria for CFS (Sharpe *et al.*, 1991), recruited from King's College Hospital or Great Ormond Street Hospital undertook the experimental tasks. Thirty one adolescents diagnosed with asthma undertook the tasks. Seventy eight healthy control participants recruited from local schools undertook the experimental tasks. However, there were two adolescents with CFS who did not complete the social performance task (1 refused to do the task as he was too nervous, the other left the session at the break). The final numbers for that task were 60 adolescents with CFS. Only 61 adolescents with CFS completed the exercise task. All participants were aged 11-18 years and did not differ on age, gender or ethnicity.

Procedure

Symptom Focusing

Symptom Focusing vs. Distraction Task

An adapted version of a symptom-focused (rumination) versus distraction task was used. This has been used extensively in depression research to compare ruminative processing and distraction (e.g. (Lyubomirsky & Nolen-Hoeksema, 1993)). In this

adapted version, participants were asked to read a list of prompt words which focus on either images or symptoms related to CFS (rather than symptoms of depression). Only the symptom focusing items, not the distraction items were changed. They were asked to use the prompt to focus either on distracting images such as a yellow boat sailing across a blue sea or on their physical and mental sensations such as fatigue. Participants within each group were randomised to either distracting images or symptom focusing. In the symptom-focusing condition, participants were asked to use their imagination and concentration to think about the causes, meanings and consequences of the items and to spend a few moments visualising and concentrating on each item, attempting to make sense of and understand the issues raised by each item. In the distraction condition, the participants were asked to focus their attention on each of the ideas on the pages. They were instructed to use their imagination and concentration to focus their mind on each experience.

A researcher not involved in the study used a random numbers table (https://stattrek.com/Tables/Random.aspx) to create a series of 80 CFS cards, 80 healthy control cards and 30 asthma cards stating the group allocation ("symptom focusing", or "distraction"). Each card was placed in a separate envelope and these were numbered. The envelope for each participant was opened by the researcher immediately prior to the task session so that the researcher was blind to the allocation until the time of arrival but could prepare the relevant task material. Participants in both conditions were told to try their best to think about each of the ideas on the pages they were given (2 pages including a repeat of the instructions). The task continued for 8 minutes. The researcher left the room for the 8 minutes of the task, in line with a previous procedure using this methodology (Lyubomirsky & Nolen-Hoeksema, 1993). A copy of the task is in

appendix 13 (page 471). Before and after completing the task, the adolescents were asked to complete Visual Analogue Scales (VAS) rating how they were feeling. All of the questions and when they were asked are listed below. The results of the first 3 items are reported in the main thesis text, the latter items are reported in appendix 14 (page 475):

- How mentally fatigued are you feeling at this moment in time?
- How physically fatigued are you feeling at this moment in time?
- How are you feeling at this moment in time? Anxious
- How happy are you feeling at this moment in time?
- How sad are you feeling at this moment in time?
- How concerned are you about your symptoms at this moment in time?
- How much pain are you feeling in your body at this moment in time?

Additional post-task VAS for a manipulation check:

- What proportion of time did you spend on the task?

Pre-performance expectations and anxiety and Post-performance self-evaluation

Visual Analogue Scales – measures completed during the task session

Before and after completing all experimental tasks, as well as at baseline (soon after arrival at the task session), the adolescents were asked to complete 0-100 VAS to rate their performance, perceived difficulty before and after the task and other task specific ratings. These are shown in appendix 15 (page 482).

Discrepancy scores

Discrepancy scores were calculated for the attention task and exercise task in order to investigate actual versus perceived performance. Objective scores (time taken) were converted into a standardised score using syntax for SPSS for both the attention task and the exercise task. Discrepancy scores for the social performance task were taken from self-rating and observer ratings on the speech evaluation questionnaire (Harvey *et al.*, 2000); to investigate post-performance self-evaluations against objective measures. These scores are explained further in the 'statistical analyses' section.

Attention task (Letter Cancellation Task)

The Letter Cancellation Task is a pen and paper task, requiring the participants to strike through the letter H in a series of lines of letters (Uttl & Pilkenton-Taylor, 2001). These tasks are widely used in clinical and research settings as quick measures of attention. Uttl and Pilkenton-Taylor (2001) have produced adult norms for this scale, but there are no such reports for adolescents to date. See Appendix 16 for the task (page 484). There are two trials, where participants are asked to complete the task as quickly as possible. It is an attention test that examines the participant's ability to pick out targets (letters H) among distractors. The specific aspects of attention it measures are sustained attention and focused attention. The participants all completed a practice form, where they were shown for the first time the several rows of letters. Their task was to find the letter H and each time they found a letter H they were instructed to cross it out with a pencil. They were told to try and work as quickly as they could, crossing out all Hs and to cross no other letters. They were timed to complete trial 1. Trial 2 was administered in exactly the same fashion after allowing the participant a brief rest (approximately 30 seconds).

The objective measurements of this task were 'time taken on task' and also 'number of errors made'.

All participants were asked to complete Visual Analogue Scales (VAS) before and after the letter cancellation task to rate aspects of their performance and how they were feeling. These were explained further in the VAS section earlier in this methodology section, on page 199 but were used to investigate pre-performance expectations and anxieties as well as post-task performance evaluation.

Exercise Task

A five-repetition sit-to-stand task (Csuka & McCarty, 1985) was used to investigate expectations and evaluations about exercise. Participants were asked to rise to standing and return to sitting as quickly as possible, five times. This is widely used as a predictor of physical functioning (e.g. (Gill *et al.*, 1995)). The task and longer versions has been found to be acceptable in chronic illness in adults (e.g. (Newcomer *et al.*, 1993)) and piloting indicated that this short version is acceptable to adolescents. Two trials were completed by all participants. Subjects were provided sufficient time between trials to feel fully recovered (approximately 30 seconds). A record was made of the time taken to complete the task. After completing the exercise task, all participants were asked to complete the Borg scale (appendix 17, page 487) to measure the participant's perceived exertion on the exercise task.

Social Performance Task

Participants were asked to give a three minute speech to the experimenter, which they were told would be videotaped. The participants were all told in standardised instructions that the experimenter would be evaluating their performance and that a video was being made to allow an evaluation of their performance by other researchers at a later point. In order to equate for prior knowledge of the topic, participants were asked to choose a topic of their own selection and given five minutes to prepare (Rapee & Lim, 1992). This social performance task (which has been used in previous research, e.g. (Harvey *et al.*, 2000)) was chosen in order to elicit some degree of stress in participants, but to a degree that would be manageable. The task has previously been used with adolescents.

The Trier social stress test (TSST) (Kirschbaum *et al.*, 1993), another stress-induction paradigm that involves a social performance task was not used as the task previously given to children was targeted at children younger than this study and likewise the task for adults was work-related and judged to be too old for this study population.

After the task (and related VAS), an explanation of the purpose of this task was given to participants, and they had the opportunity to talk about their feelings about doing the task.

Psychological responses to the task were assessed using the STAIC-S (state anxiety measure; appendix 18, page 488) before introduction to the task and after the presentation. After the task, adolescents also completed the Speech Evaluation Questionnaire ((Harvey *et al.*, 2000); appendix 19, page 489) which included positive and negative indicators of performance (e.g. understandable, confident, clear voice,

awkward, blushed). Raters who were blind to the participant group subsequently rated the videos on the same questionnaire and this is described in more detail below.

- Observer ratings of social performance task

To assist in investigating the discrepancy hypotheses of post-performance evaluation / discrepancy scores on this task, each participant was filmed during the 3 minute social performance task, so that they could be rated, by independent raters for performance. As described above, participants were told this was happening, which is designed to add to the stress of the situation. The independent raters were four research assistants from the CFS service, where 2 raters separately rated each video. They rated each of the videos using the speech evaluation questionnaire (Harvey *et al.*, 2000). This is the same measure completed by the participants and allows a direct comparison. An average of the scores for the 2 raters was used.

Attribution of symptoms of stress

In addition to the standard VAS completed, to measure participants' attributions to the stress experienced surrounding the social performance task, participants with CFS or asthma were asked to complete a further set of VAS. These recorded any subjective, physiological experience of stress i.e. symptoms, and to what they attributed it. The options were; to the task, to their health or to something else. They were asked to complete the 0-100 VAS by rating on the scale as before and then in corresponding boxes they were asked to tick whether the specific symptom was due to their illness, the stress of the task or something else. If they ticked something else, they were asked to

specify what it was. They could also tick more than one box if they felt it was appropriate.

The additional questions were:

- How do you feel now? Sweaty hands
- How do you feel now? Heart beat
- How do you feel now? Nervous
- How difficult is it to think clearly?
- How difficult is it to find the correct words?

Physiological measures of skin conductance, heart-rate and cortisol levels were taken during the task session, specifically around the social performance task and in anticipation of the exercise task and are reported in full in chapters 6 and 7.

Parental expectations

Parents were also asked to make the same ratings on how they felt their child would feel and perform on the performance tasks. They were asked to make these ratings on the day of the experimental tasks with the researcher (author), whilst the child was not in the room.

Data preparation and Statistical Analyses

Tests for normality were conducted to identify which statistical tests should be used. According to the Q-Q plots and histograms, the data was normally distributed and met assumptions for parametric analyses.

Symptom focusing vs. distraction task

For the symptom-focusing task, 2*3*2 repeated measures ANOVAs with time as the within-subjects variable and group (CFS versus asthma versus healthy) and condition (symptom focusing versus distraction) as the between-subject variables were used to investigate changes over time both within and between subjects. One-way ANOVAs and paired t-tests were conducted where necessary to explore main effects or interactions as appropriate.

Pre-performance expectations and anxiety

To compare groups on pre-performance expectations, one-way ANOVAs were conducted.

Post-performance evaluation

To compare groups on post-performance self-evaluation, one-way ANOVAs were again used. In order to address the post-performance self-evaluation, discrepancy scores were calculated. To do this, on the attention and exercise tasks, a standardised score for time taken (and errors made in the attention task) was created in SPSS. A one-way ANOVA was used to investigate any differences between the 3 groups for this discrepancy score. For the social performance task, the discrepancy scores were calculated using the self- and independent ratings on the speech evaluation questionnaire (SEQ). This subjective (VAS) rating for how well the participant thought they did on the task was then subtracted from the objective score (objective – subjective).

For the objective measures on the performance tasks, a one-way ANOVA was used to compare the groups. Given the significant difference between groups on IQ (see Chapter 3; p=.003*, with the CFS group having significantly lower IQ than the control groups), this was controlled for in the analyses for the actual performance on the letter cancellation task. This analysis was conducted using an analysis of covariance (ANCOVA).

Correlations between time taken on task (Letter cancellation task [LCT] and exercise task [ET]) as well as errors made (LCT only) and perceived performance were investigated and tabulated (see appendix 20, page 492 and 21, page 494 for LCT and appendix 23 for ET, page 497). Exercise task performance and correlations with the clinical questionnaires measures are also included in appendix 24 (page 498) for reference.

Attributions of symptoms of stress

Chi-squared tests were used to investigate the attributions of symptoms of stress in the asthma and CFS groups. Only cells with more than 5 counts per cell were included in the analysis. As mentioned earlier in the methodology, participants could tick more than one box (both illness and stress of the task) and an extra variable was subsequently created for this in SPSS. Those participants that ticked 'none', implying that they were not experiencing any symptoms were then excluded from the analyses.

Parental expectations

One-way ANOVAs were used to compare the parents in each of the 3 groups on VAS ratings. Parent and child correlations on the VAS were also conducted (see tables in

appendix 22, page 496). The same analyses were repeated using ANCOVAs to control for both maternal occupation and maternal GHQ scores (chapter 4).

Results

Symptom Focusing vs. Distraction Task

Manipulation check: "What proportion of time did you spend on the task?"

Participants were asked to rate what proportion of time they spent focusing on the task. The mean ratings and group comparisons are in table 5.2. A 2x2 ANOVA revealed a significant group difference, with post-hoc tests indicating that the CFS group and healthy controls focused significantly more than the asthma group on the task. There was also a significant effect of condition so that overall there was greater time spent on task during the symptom focusing condition. Post hoc tests revealed the significant differences were in the asthma group and healthy control groups, where they focused significantly less on the task when randomised to the distraction condition. These differences were not apparent in the CFS group.

Table 5.2: Symptom focusing vs. distraction task; Time spent focusing on task (rated on 0-100 VAS)

	Symptom Focusing	**Distraction**	**Result**
	Mean (SD)	Mean (SD)	**2x2 ANOVA**
CFS	58.15 (21.55)	59.43 (24.49)	Group: F(2,165) = 9.93, p = .000*
Asthma	50.13 (24.35)	19.33 (39.86)	Condition: F(1,165) = 11.19, p = .001*
Healthy Controls	71.30 (27.16)	52.22 (31.90)	Group*Condition: F(2,165) = 3.65, p = .028*

Does symptom-focusing increase symptoms of fatigue?

Table 5.3 shows the VAS results for all groups. Given the large number of analyses contained in a 2x3x2 ANOVA, only the key predictions and significant results are displayed. For a full breakdown of the analyses, please refer to appendix 20 (page 492). Contrary to predictions, there were no significant three-way interactions between Group, Time and Condition.

For **physical fatigue**, there was a Time by Condition interaction; post-hoc tests indicated an increase in physical fatigue in the symptom-focusing condition, with no significant change in the distraction condition within groups. For **mental fatigue** there was a Time by Group interaction, with post-hoc tests indicating that the CFS and asthma groups increased significantly in mental fatigue but the healthy controls did not across conditions. The CFS group had significantly higher scores than the other two groups for mental fatigue at both time points. For **pain**, there was a significant group by time interaction. Here, the CFS group increased significantly but the other two groups did not. The CFS group had significantly higher scores for pain than the other two groups at both time points.

Table 5.3: Visual analogue scales for symptom focusing vs. distraction task; pre- and post-task means, standard deviations and repeated measures ANOVAs

		CFS		**Asthma**		**Healthy control**		**Result**
		Pre	**Post**	**Pre**	**Post**	**Pre**	**Post**	**2x3x2 RM ANOVA**
How mentally fatigued are you feeling at this moment in time?	Symptom focusing	42.29 (24.17)	50.74 (26.37)	14.06 (18.45)	19.75 (14.85)	22.57 (21.42)	27.73 (22.90)	**Within subjects effects:** **Time: F(1,163) = 14.43, p = .000*** **Time*group: F(2,163) = 3.05, p = .050*** **Between subjects effects: F(2,163) = 29.66, p = .000***
	Distraction	50.21[a] (24.38)	55.46[a] (25.30)	15.13 (15.96)	28.00 (24.25)	27.85[a] (22.55)	24.66[a] (21.51)	
How physically fatigued are you feeling at this moment in time?	Symptom focusing	39.79[a] (26.76)	41.85[a] (27.83)	15.88 (16.31)	24.19 (20.15)	16.24[a] (19.24)	18.27[ab] (20.29)	**Within subjects effects:** **Time*condition: F(1,165) = 7.04, p = .009*** **Between subjects effects: F(2,165) = 30.45, p = .000***
	Distraction	49.68[b] (24.56)	51.29[b] (25.83)	20.60 (27.91)	13.33 (17.80)	20.76[b] (22.52)	19.20[b] (20.52)	
How much pain are you feeling in your body at this moment in time?	Symptom focusing	27.44 (20.97)	32.24[a] (24.45)	10.06[a] (16.83)	11.88[a] (17.25)	9.00[a] (11.50)	7.59[a] (8.65)	**Within subjects effects:** **Time*group: F(2,163) = 4.03, p = .020*** **Between subjects effects: F(2,163) = 39.98, p = .000***
	Distraction	34.75[a] (28.10)	34.32[a] (29.64)	2.15 (4.45)	10.53[a] (22.79)	6.78[a] (10.31)	5.80[a] (10.03)	

[ab] Values that have the same superscript are not significantly different from each other.

Pre-performance expectations and anxiety

1) How well do you think you will do on the task?

Table 5.4 presents the VAS data for how well the participants thought they would do on the different tasks. The healthy control group expected to perform significantly better than either of the other two groups on the attention task and the social performance task. On the exercise task, the CFS group expected to perform significantly worse than either of the other two groups.

Table 5.4: Visual Analogue Scale analyses for expected performance on the performance tasks; means standard deviations and results of the one-way ANOVAs

	Participant group	**Pre-task Mean (SD)**	**Results of the one-way ANOVAs**
Attention task	CFS	64.26 (15.35)[a]	**F(2,168) = 3.17, p = .042***
	Asthma	62.68 (25.52)[a]	
	Healthy Controls	70.50 (15.72)	
Social performance task	CFS	45.13 (20.22)[a]	**F(2,166) = 10.48, p = .000***
	Asthma	47.71 (25.70)[a]	
	Healthy Controls	61.15 (20.83)	
Exercise task	CFS	52.56 (18.47)	**F(2,158) = 9.08, p = .000***
	Asthma	64.00 (18.04)[a]	
	Healthy Controls	67.64 (19.71)[a]	

[a] values that have the same superscript letter are not significantly different from each other

2) How difficult do you think you'll find the task?

Table 5.5 shows the results of the ANOVAs for how difficult participants expected to find the task. The CFS group expected the social performance task and the exercise task to be significantly more difficult than the other two groups. There was no significant difference between the groups on how difficult they expected the attention task to be.

Table 5.5: Visual Analogue Rating Scales analyses for how difficult participants expected to find the task; means, standard deviations and one-way ANOVAs

	Participant group	**Pre-task Mean (S.D.)**	**Results of repeated measures ANOVAs**
Attention task	CFS	29.29 (18.95)[a]	F(2,168) = .86, p = .425
	Asthma	25.39 (21.37)[a]	
	Healthy Control	25.09 (19.73)[a]	
Social performance task	CFS	55.05 (20.31)	**F(2,166) = 12.61, p = .000***
	Asthma	37.42 (25.68)[a]	
	Healthy Control	36.00 (24.11)[a]	
Exercise task	CFS	43.24 (25.31)	**F(2,155) = 27.41, p = .000***
	Asthma	17.86 (16.52)[a]	
	Healthy Control	18.33 (17.08)[a]	

3) How anxious are you at this moment in time?

All participants were asked pre-task to rate how anxious they were. Table 5.6 presents the results of the ANOVAs. The CFS group were significantly more anxious than the other two groups at the pre-task ratings for the social performance task as well as the exercise task. There were no differences between groups on anxiety before the attention task.

Table 5.6: Means, standard deviations and one-way ANOVAs for how anxious the participants were, pre-task for all performance tasks

	Participant group	**Pre-task Mean (S.D.)**	**Result (one-way ANOVA)**
Attention task	CFS	23.63 (18.08)[a]	F(2,168) = .43, p = .650
	Asthma	21.28 (20.96)[a]	
	Healthy Control	20.62 (19.81)[a]	
Social performance task	CFS	46.00 (27.15)	**F(2,166) = 3.77, p = .025***
	Asthma	34.90 (29.84)[a]	
	Healthy Control	33.82 (25.63)[a]	
Exercise task	CFS	28.07 (22.71)	**F(2,155) = 6.13, p = .003***
	Asthma	16.93 (18.50)[a]	
	Healthy Control	16.88 (16.26)[a]	

[a] values that are the same superscript letter are not significantly different from each other

4) How well do you think you will be able to concentrate on the attention task?

Table 5.7 shows the results of the ANOVA for how well the participants thought they would be able to concentrate on the attention task. Here, the CFS group expected their concentration on the task to be significantly worse than the two control groups.

Table 5.7: Visual Analogue Scale analyses for how well participants thought they would be able to concentrate on the attention task; means standard deviations and results of the one-way ANOVA

	Participant group	**Pre-task Mean (S.D.)**	**Result (one-way ANOVA)**
Attention task	CFS	58.19 (18.05)	**F(2,168) = 22.36, p = .000***
	Asthma	71.21 (21.69)[a]	
	Healthy controls	78.38 (15.79)[a]	

All of the above analyses were repeated controlling for IQ, given that there was a significant difference on IQ between the groups (see chapter 3). However, all results remained the same, with no changes in significance on the variables.

Post-performance self-evaluation

Results will be presented in the following order; A) objective performance and discrepancy scores for each performance task, followed by B) post-performance ratings / self-evaluation.

A) Objective performance and discrepancy scores

1) Attention task

- Objective performance

See table 5.8 for results of repeated measures ANOVAs for objective performance on the attention task. There was a significant difference between the groups on time taken on the attention task, with the CFS group taking significantly longer than both control groups. There was also a within subjects effect of time, with all groups taking less time to complete the second trial than the first. There were no main effects or interactions regarding the number of errors made.

When controlling for IQ, the significant differences of time remained; trial 1 ($F(2,166) = 10.34$, $p = .000$)* and the same for trial 2 ($F(2,166) = 10.04$, $p = .000$)*, with the CFS group taking significantly longer than the other two groups on both trials.

Table 5.8: Group comparisons for the objective measures of the attention task: Means and Standard deviations and results of repeated measures ANOVAs

	Chronic Fatigue Syndrome (N=62)	**Asthma (N=31)**	**Healthy Controls (N=78)**	**Results of repeated measures ANOVAs**
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	
Trial 1 – time taken	56.27 (20.96)	45.68 (10.85)[a]	44.78 (10.21)[a]	Within subjects: Time: F(1,168) = 12.70, p = .000* Group*time: F(2,168) = 1.33, p = .266 Between groups: F(2,168) = 11.53, p = .000*
Trial 2 – time taken	55.4 (25.67)	42.26 (8.26)[a]	42.67 (9.8)[a]	
Trial 1 – errors made	.94 (1.35)	1.19 (2.01)	.87 (1.33)	Within subjects: Time: F(1,168) = .25, p = .619 Group*time: F(2,168) = .22, p = .806 Between groups: F(2,168) = .36, p = .701
Trial 2 – errors made	1.05 (1.66)	1.13 (1.23)	1.0 (1.26)	

[a] values that have the same superscript letter are not significantly different from each other.

- Discrepancy between post-task performance rating and actual performance on the attention task

Time taken on task was converted into a standardised score (described in statistical analyses section). One-way ANOVAs revealed that there were no significant differences between groups on the discrepancy scores; for how well they thought they had performed on the task and their actual performance (time taken), for either trial. Table 5.9 shows the results. A positive score indicates a higher score on the objective measure and lower score on the subjective rating. A negative score indicates a lower score on the objective measure than the self-rating.

Table 5.9: Discrepancy scores for the actual and perceived performance on the attention task

		CFS	Asthma	Healthy Control	Results
Time taken Trial 1 and how well do you think you did	Post-task	3.55 (22.15)	-7.35 (27.14)	.760 (18.76)	F(2,166) = .09, p = .917
Time taken Trial 2 and how well do you think did	Post-task	6.41 (25.59)	3.72 (23.57)	4.03 (17.86)	F(2,166) = .25, p = .780

A one way ANOVA was also completed for the number of errors made as the objective score and perceived performance as the subjective rating in the discrepancy analyses. One-way ANOVAs revealed that there were no significant differences between groups on the discrepancy scores; for how well they thought they had performed on the task and their actual performance in terms of errors made, for either trial.

2) Social performance task

- Independent ratings

Independent observer ratings of social performance were lower for the CFS participants than for the other two groups (see Table 5.10).

- Self-ratings

There was a significant difference between the groups on the speech evaluation questionnaire (SEQ). The CFS group rated their performance significantly worse than the healthy control group and the asthma group.

- Discrepancy scores: Subjective self-ratings and Objective independent raters - Speech Evaluation Questionnaire

A discrepancy score was calculated (self-rating minus independent-rater) and there was not a significant difference between groups. The results are outlined in table 5.10.

Table 5.10: Speech evaluation Questionnaire results (self-rating and independent-rater comparisons); means, standard deviations, and one-way ANOVAs

	Chronic Fatigue Syndrome	**Asthma**	**Healthy Controls**	**Results**
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**One-way ANOVAs**
Speech Evaluation Questionnaire (self)	77.14 (24.47)	88.60 (29.10)[a]	94.40 (26.03)[a]	F|(2,135) = 6.45, p = .002*
Speech Evaluation Questionnaire (rater)	84.97 (22.71)	94.78(10.49)[a]	94.27 (16.99)[a]	F(2,149) = 4.47, p = .013*
Discrepancy score	-5.44 (26.10)	-3.83 (30.59)	-0.74 (25.61)	F(2,117) = .42, p = .660

3) Exercise task

- Objective performance

First, there was a significant group by time interaction for objective performance (time taken). The post-hoc analyses revealed the CFS group took significantly longer than both of the control groups on both trials of the exercise task. Further, the CFS and healthy control groups took significantly less time to complete the second task to the first. There were no differences between the healthy controls and the asthma group.

- Discrepancy scores

Discrepancy scores were calculated for objective and subjective performance on the exercise task. See table 5.11 for the results of these ANOVAs. The bottom row of the table indicates that there was not a significant difference between the groups on the discrepancy scores. In table 5.11 a positive score indicates a higher score on the objective measure and lower score on the subjective rating. A negative score indicates a lower score on the objective measure than the self-rating.

Table 5.11: Means, standard deviations and repeated measures ANOVAs for the time taken on the exercise task (objective measures and discrepancy scores)

	Chronic Fatigue Syndrome (N=62)	**Asthma (N=31)**	**Healthy Controls (N=78)**	**Results**
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Repeated measures ANOVA**
Trial 1 – time taken	11.40 (5.29)	7.16 (1.80)[a]	7.35 (2.10)[a]	Within subjects: F(1,156) = .018, p = .894 Group by time interaction: F(2,156) = 6.28, p = .002* Between groups: F(2,156) = 38.83, p = .000*
Trial 2 – time taken	11.02 (3.44)	7.00 (1.77)[a]	7.08 (2.13)[a]	
Discrepancy scores **(average time taken – subjective rating of how well they did)**	-15.01 (22.53)	-15.79 (19.03)	-11.37 (20.38)	F(2,155) = .70, p = .498

B) Post-performance ratings and self-evaluation

1) How well do you think you did on the task?

The healthy controls, as with pre-task, rated their performance significantly higher than the other two groups on the social performance task. The CFS group rated their performance significantly worse on the exercise task. There were no significant differences on how well the participants thought they had done on the attention task. The results of the ANOVAs are displayed in table 5.12.

Table 5.12: Visual Analogue Scale analyses for how well participants thought they did on the performance tasks; means standard deviations and results of the one-way ANOVAs

	Participant group	**Post-task Mean (SD)**	**Results of the one-way ANOVAs**
Attention task	CFS	67.11 (73.59)	F(2,168) = 2.88, p = .059
	Asthma	73.59 (21.31)[a]	
	Healthy Controls	73.77 (15.20)[a]	
Social performance task	CFS	41.84 (22.05)	**F(2,166) = 8.17, p = .000***
	Asthma	49.32 (29.43)[a]	
	Healthy Controls	58.63 (23.22)[a]	
Exercise task	CFS	54.73 (15.75)	**F(2,155) = 8.64, p = .000***
	Asthma	63.00 (19.88)[a]	
	Healthy Controls	68.67 (20.56)[a]	

[a] values that have the same superscript letter are not significantly different from each other

2) How difficult did you find the task?

The CFS group found all 3 performance tasks significantly more difficult than both of the control groups. The results of the ANOVAs are displayed in table 5.13.

Table 5.13: Visual Analogue Scale analyses for how difficult participants found the performance tasks; means standard deviations and results of the one-way ANOVAs

	Participant group	**Post-task Mean (SD)**	**Results of the one-way ANOVAs**
Attention task	CFS	32.24 (23.18)	**F(2,168) = 4.05, p = .019***
	Asthma	19.00 (20.15)[a]	
	Healthy Controls	24.08 (22.87)[a]	
Social performance task	CFS	57.03 (24.79)	**F(2,166) = 11.23, p = .000***
	Asthma	32.39 (26.80)[a]	
	Healthy Controls	39.41 (27.42)[a]	
Exercise task	CFS	38.80 (24.72)	**F(2,155) = 51.07, p = .000***
	Asthma	8.39 (9.40)[a]	
	Healthy Controls	10.12 (12.16)[a]	

[a] values that have the same superscript letter are not significantly different from each other

3) How anxious are you feeling at this moment in time?

All adolescents were asked to rate how anxious they were immediately after finishing the performance tasks. The results of the ANOVAs are shown in table 5.14. The CFS group were significantly more anxious post-task on both the social performance task as well as the exercise task, in comparison to both control groups. There were no differences between groups on levels of anxiety after the attention task.

Table 5.14: Visual Analogue Scale analyses for how anxious participants were immediately after the performance tasks; means standard deviations and results of the one-way ANOVAs

	Participant group	**Post-task Mean (SD)**	**Results of the one-way ANOVAs**
Attention task	CFS	21.00 (17.75)[a]	F(2,168) = 1.77, p = .174
	Asthma	14.26 (18.55)[a]	
	Healthy Controls	17.18 (16.14)[a]	
Social performance task	CFS	36.26 (26.65)	**F(2,164) = 4.77, p = .010***
	Asthma	22.06 (20.64)[a]	
	Healthy Controls	26.09 (21.60)[a]	
Exercise task	CFS	24.60 (21.87)[a]	**F(2,155) = 15.18, p = .000***
	Asthma	6.68 (11.72)[a]	
	Healthy Controls	10.95 (13.01)[a]	

[a] values that have the same superscript letter are not significantly different from each other (post task)

4) How well were you able to concentrate on the attention task?

All participants were asked to rate how well they were able to concentrate on the attention task. The CFS group reported that their concentration was significantly worse than the other two groups on this task. Results of the ANOVA are shown in table 5.15.

Table 5.15: Visual Analogue Scale analyses for how well participants thought they were able to concentrate on the attention task; means, standard deviations and results of the one-way ANOVA

		Mean (S.D.)	**Result (one-way ANOVA)**
Attention task	CFS	60.97 (20.46)	**F(2,168) = 13.25, p = .000***
	Asthma	72.29 (29.32)[a]	
	Healthy controls	79.26 (16.95)[a]	

Attributions of symptoms of stress

Table 5.16 displays the chi-squared analyses for attributions of physiological dysregulation in relation to the social performance task. Participants in the CFS group attributed difficulty thinking clearly and difficulty finding the correct word significantly more to their illness than stress of the task than the asthma group. Other symptoms were not different across groups. Only variables with five or more counts per cells were used for the chi-squared analyses. All percentages are included in the table for reference.

Table 5.16: Attributions for the physiological dysregulation on the Social Performance Task; chi-squared tests between the CFS and asthma groups

Attributions		CFS (n=57)	Asthma (N=22)	Result (X^2)
Sweaty	None	-	-	X^2 (3,30) = 2.846, p = .416
	Illness	-	-	
	Stress of the task	75.0	75.0	
	Other reasons	17.7	25.0	
	Both stress and illness	8.3	-	
Heart Beating	None	-	14.3	X^2 (4,33) = 5.308, p = .257
	Illness	4.2	71.0	
	Stress of the task	87.5	78.6	
	Other reasons	4.2	-	
	Both stress and illness	4.2	-	
Nervous	None	-	-	X^2 (4,41) = 2.950, p = .566
	Illness	-	-	
	Stress of the task	92.0	92.3	
	Other reasons	8.0	7.7	
	Both stress and illness	-	-	
Difficulty to think clearly	None	-	6.7	**X^2 (3,41) = 11.373, p = .010***
	Illness	36.0	13.3	
	Stress of the task	24.0	80.0	
	Other reasons	4.0	-	
	Both stress and illness	36.0	-	
Difficulty finding the correct word	None	-	21.4	**X^2 (4,38) = 21.005, p = .000***
	Illness	36.0	-	
	Stress of the task	48.0	78.6	
	Other reasons	-	-	
	Both stress and illness	16.0	-	

Parent rating Scales

Results of one-way ANOVAs comparing parental ratings of how well they thought their child would do on the performance tasks, how difficult they would find them, as well as mental and physical fatigue and anxiety across the three groups for the three performance tasks are shown in appendix 25, page 499. The key results are reported here.

On all 3 tasks (attention, exercise and social performance), the parents of the adolescents with CFS expected that their child would find the task significantly more difficult, and would have significantly higher mental and physical fatigue before the task and significantly higher anxiety. On the social performance task and the exercise task, the parents of the adolescents with CFS expected that their child's performance would be significantly worse than the other two groups. On the letter cancellation specific question on concentration, the parents of the adolescents with CFS expected that their child would have significantly worse concentration than the other two parent groups. The findings remained when controlling for GHQ score in the mother and occupational status of the mother (Davis-Kean *et al.*, 2001).

Discussion

The aim of this chapter was to experimentally investigate possible maintaining factors in CFS in adolescents. This included symptom focusing, pre-performance expectations and anxiety, post-performance self-evaluation, attributions of symptoms of stress and parental expectations about performance. The findings will be discussed in relation to

the previous literature and models of CFS. Clinical implications of the results will be presented.

Symptom focusing

Does symptom focusing increase symptoms of fatigue?

The hypothesis that focusing on the causes, meanings and consequences of one's current symptoms, compared to distraction, would result in significantly larger increases in fatigue in the CFS participants than the control groups was not supported. All three groups showed an increase in physical fatigue in the symptom focussing condition but no significant change in the distraction condition. In contrast, for mental fatigue and pain there was no difference between symptom-focusing and distraction conditions. Regardless of condition, the CFS participants showed an increase in both mental fatigue and pain, the asthma groups showing an increase in mental fatigue whereas the healthy controls showed no significant change over time.

Unsurprisingly, the CFS group had higher scores for mental and physical fatigue and pain before and after the task than the other two groups. Cognitive behavioural models of CFS in adults (e.g. (Surarwy *et al.*, 1995)) suggest that focusing on symptoms intensifies the symptom experience. This study provides evidence for this in the adolescent population for physical fatigue, and these results indicate that effect occurs for adolescents with CFS, asthma and healthy individuals.

The findings indicate that for participants with CFS, tasks that require concentration on either symptoms or mental images are associated with an increase in mental fatigue. This finding is not necessarily surprising given clinical reports that concentrating is

tiring for individuals with CFS. However, it is unclear why the asthma participants also show an increase in mental fatigue regardless of condition whereas the healthy individuals do not.

The task used in this study has been widely used to investigate analytical self-focused attention in depression (Nolen-Hoeksema, 1991). Contrary to the current study, in studies of depressive self-focussed attention control participants' mood was not affected by the symptom focusing items they were concentrating on. One reason for this difference could be that the control participants in the current study were more likely to be experiencing some degree of fatigue-related symptoms on which they were asked to focus than the participants in the previous studies. In previous studies, the control participants may have been less likely to be currently experiencing symptoms relating to depression. It has been shown in other domains that when focusing a person's attention on certain symptoms, their reporting of symptoms associated with this increases (Pennebaker & Skelton, 1978). People tend to report more physical symptoms (Pennebaker, 1982) and experience a higher intensity of emotion (Carver, 1978) when attention is directed towards symptom experience.

Pre-performance expectations

All participants were asked to give pre-task expectations of their performance on the experimental tasks. On the exercise task and the social performance task, the CFS group expected to do significantly worse, and to experience greater difficulty than both control groups. On the attention task, the healthy control group had significantly higher expectations of their performance than either of the other two groups, but there were no significant differences between the groups on expected difficulty. The CFS group

expected concentration to be significantly worse than either of the other two groups on the attention task. The results from this study do suggest that the adolescents with CFS had lower expectations for performance, as hypothesised. This could be because they felt they could not achieve things to the level they once had. They were possibly attributing previous performance difficulties to their having CFS. This was particularly apparent in relation to the exercise and social performance tasks. This supports the findings of previous studies (Fry & Martin, 1996; Garralda & Rangel, 2001; Godfrey *et al.*, 2009). Each reported unrealistic perceptions and inaccurate expectations of performance. It remains unclear why certain tasks are expected to be more problematic than others. Further research is warranted.

Cognitive behavioural models suggest that adults with CFS have developed unhelpful beliefs about the consequences of exercise (Surarwy *et al.*, 1995). Wessely et al. (1989) proposed that the individual starts to reduce their activity levels in an understandable attempt to feel less fatigued, but in fact their exercise tolerance worsens. Fatigue subsequently increases when they try to do more. Beliefs such as "There must be something seriously wrong with me" and "If I continue with this activity I will end up feeling worse", contribute to activity reduction and avoidance. Adolescents are fearful of exercise as they believe it will exacerbate their symptoms. The following chapter will assess the extent to which self-report measures of fear correspond to more objective measures of arousal (e.g. heart rate). This will improve our understanding, as self-reports of activity levels are not necessarily entirely reliable (Fry & Martin, 1996).

Pre-performance anxiety

The CFS group were significantly more anxious prior to the social performance task and the exercise task than either of the other two groups. There were no differences between groups for pre-task anxiety on the attention task. This finding, in line with the pre-performance expectations, suggests that there are specific concerns for the adolescents with CFS about doing exercise and performance tasks. The CFS group may have been more anxious on the social performance task than the other two groups as social skills can be problematic for some adolescents with CFS. This problem with social skills was reported by the mothers in the CFS group in comparison to the controls using the ASQ (Baron-Cohen *et al.*, 2001) (chapter 3). With the higher self-reported levels of anxiety in this population (chapter 3), it is unsurprising that on a social stress task the levels of anxiety are higher. One must consider that the young person may have been out of the educational system for some time which will likely have resulted in a loss of confidence socially.

Post –performance self-evaluation

The CFS participants performed more poorly than the other two groups on the social performance and exercise task. For the attention task they had no more errors but took longer than the control groups. These results are consistent with clinical reports of impaired functioning across different areas of functioning for people with CFS. It was hypothesised that the discrepancy between self-evaluation of performance and objective ratings would be larger in the CFS group than either of the other two groups; their self-ratings would be more negative relative to objective ratings. This hypothesis was based on cognitive behavioural models which suggest that negative aspects of perfectionism

are associated with critical performance self-evaluation (Shafran *et al.*, 2002). However, this prediction was not supported. For each of the three tasks, the CFS participants rated their performance significantly more negatively than the control groups. However, there was no evidence of a greater discrepancy between objective ratings and subjective ratings across the groups. Therefore the CFS participants appeared to be fairly accurately judging their level of performance – there was no evidence that they were being overly self-critical.

These findings contrast to a previous study in which Metzger & Denney (2002) reported that CFS patients consistently underestimated their performance on a neuropsychological test when compared to healthy controls.

Attributions of symptoms of stress

Adolescents with CFS and adolescents with asthma were asked to attribute increased physiological dysregulation in relation to the social performance task to 'stress', 'illness', 'both', or 'other' factors. In the CFS group, the cognitive constructs; 'difficulty to think clearly' and 'difficulty finding the correct word' were attributed significantly more to the illness rather than the stress of the task, in comparison to the asthma group. Wessely *et al.* (1989) proposed that this misattribution of symptoms to illness can lead to fearful and catastrophic beliefs about engaging in activity and an avoidance of activities which may exacerbate symptoms. It has been suggested in cognitive behavioural models of CFS in adults (Surarwy *et al.*, 1995), that this tendency to make somatic attributions is due to beliefs about negative emotions (stress) being unacceptable and a sign of weakness. An unhelpful way of thinking about stress may act to perpetuate the patient's reduced functioning. For example, if the symptoms of stress

are misattributed to illness, they may deliberately withdraw from activities (e.g. school) if they conclude that such activities are causing their CFS to worsen. This may also contribute to symptom focusing and help-seeking behaviours, and means that the underlying cause of stress is not addressed.

Cross-sectional research (e.g. (Garralda & Rangel, 2001)) reported that adolescents with CFS most frequently attribute their CFS to a biological cause. This study has added evidence to the literature suggesting that adolescents with CFS misattribute symptoms of stress to their illness. Seemingly they are overlooking how external demands may be resulting in stress and increased physical symptoms as a result. CBT interventions typically already include educating the adolescent about stress and enabling them to deal with it more effectively.

Parental ratings

In this current study, on all tasks, parents of adolescents with CFS reported that their children would find the performance tasks significantly more difficult, have higher levels of mental and physical fatigue and anxiety than the parents in the other two groups. These lower expectations could result in worse performance and reduced activity in the child due to less being expected of them. This reduced activity could contribute to negative beliefs about engaging in activity for fear of making symptoms worse. One must consider that if parental goals are not in line with what the individual may realistically achieve or want to achieve and these expectations are expressed to the child, the result may be avoidance of future attempts. This would consequently lower future performance or indeed expectations thereof.

Previous studies in the general population investigating parental expectations of their child's performance have reported that family socio-economic variables are significant predictors of parental expectations (e.g. (Davis-Kean *et al.*, 2001)). These authors reported that parents had higher expectations if the parent's socioeconomic situation was higher. In addition, how parents feel about the self has also been shown to influence parental expectations for the child (e.g. (Kaplan *et al.*, 2001)). Given these findings, the current study controlled for maternal occupation and GHQ score when investigating parental expectations. The findings in this study remained when controlling for these factors.

Clinical Implications

The current findings suggest that focusing on symptoms in an analytical way, thinking about the causes, meaning and consequences of the symptoms, is associated with an increase in mental and physical fatigue and pain. CBT could include behavioural experiments to help patients observe the consequences of different ways of processing their ongoing experience.

Negative beliefs about activity as well as avoidance behaviour towards exercise could influence the performance on exercise tasks (Nijs *et al.*, 2008). It is possible that if the patients with CFS expect exercise to be difficult or result in higher levels of fatigue, then they would avoid them, or indeed perform less well overall. This has been shown in adults with CFS (Vercoulen *et al.*, 1998). This might affect engagement with interventions such as CBT and graded exercise therapy which both encourage increases in activity levels. It would be useful to measure whether changes in beliefs about activity and exercise mediate changes in performance after a course of CBT or GET.

The finding of the misattribution of symptoms reported in this study reinforces the current strategy within CBT to help educate the adolescent about stress and enabling them to deal with it more effectively. Furthermore, parental low expectations taken with the mother's negative beliefs about engaging in activity and their perception of the child's avoidance of activity behaviours (reported in chapter 4) imply treatment should involve the parents as well as the child. This is advocated in child and adolescent approaches to CFS (Chalder *et al.*, 2002).

Limitations

The experimental tasks used in this study are subject to some methodological limitations. For example, on the symptom focusing vs. distraction task, the asthma group and healthy control groups reported spending significantly less proportion of their time on the task if assigned to the distraction condition than the asthma and healthy controls assigned to the symptom focusing condition. It is possible that the results showing that across all groups there was greater fatigue after the symptom focusing condition may reflect this. However, there were no differences between conditions for time spent on task in the CFS group, who still showed the same pattern of increased fatigue in the symptom focusing condition and not the distraction condition. The fact that the CFS participants focused on both tasks similarly may reflect their tendency to be conscientious or perfectionistic in their approach to tasks. As recommended by previous authors (Lyubomirsky & Nolen-Hoeksema, 1993), the researcher (author) left the room for the duration of the task. It might be worth considering the advantage of staying in the room to ensure that the task is completed effectively.

The items on the speech evaluation questionnaire (completed by both adolescent and independent rater) relate to (observed) performance, rather than content or quality. For example, 'relaxed' or 'hands shaking'. It is not necessarily the case that the CFS group were not as good at the task with regards to the verbal content, but possibly that they were more socially anxious and this was reflected in the rating of specific public speaking behaviours.

The visual analogue scales (VAS) may have become repetitive by the end of the series of tasks. Participants were asked to complete the scales several times (before and after each task). It is possible that the participants did not complete the scales with full accuracy by the end of the session. However, there was no evidence that this was the case, as there were differences between the groups on the exercise task. This was the last task completed. A final limitation is that participants were not asked to rate how they 'should' perform on the tasks as well as how well they expected to do. This was in order to limit the number of questions participants were asked to complete, but it may have added another dimension to the study. For instance, Fry & Martin (1996) reported the CFS group had high expectations of post-CFS abilities.

Chapter Summary

The adolescents with CFS had lower pre-performance expectations and anxiety in comparison to the other two groups, particularly in relation to the social performance and exercise tasks. Self-evaluation of performance on tasks was also lower in the CFS group than the control groups with higher scores for experienced difficulty too, but their self-ratings were in line with their reduced objective performance. Symptom focusing increased physical fatigue compared to distraction in each of the groups. Adolescents

with CFS (mis)attributed cognitive symptoms of stress to their illness rather than the stress of the performance task. Parents of adolescents with CFS had lower expectations of the adolescents' performance. Each of these factors may also act to maintain symptoms or impairment in adolescents. The next stage will be to describe the physiological responses recorded for the social performance task and in anticipation of the exercise task to further understand physiological effects of stress in adolescents with CFS.

Chapter 6: An experimental study investigating physiological responses to stressful tasks in adolescents with CFS

Chapter Synopsis

Previous studies have reported differences in heart rate (HR) and heart rate variability (HRV) between adolescents with CFS and healthy adolescents (e.g. (Wyller *et al.*, 2007a)). One factor that may be contributing to these HR characteristics is a differential stress response in adolescents with CFS. This study investigated whether there were differences in HR, HRV and skin conductance response (SCR) in adolescents with CFS compared to healthy adolescents and adolescents with asthma. HR and SCR were measured before, during and after a social performance task and during anticipation of an exercise task.

The CFS group had a significantly higher HR in anticipation of the speech and the exercise task as well as slower HR recovery after the speech compared to the healthy and illness control groups. There was not a significant difference on baseline HR. The healthy controls were the only group to have a significant increase in HR from preparation to the performance of the speech task. The repeated measures for root mean of successive differences (RMSSD; which is a time dependent measure of HRV) revealed a significantly lower HRV at baseline in the CFS patients compared with the other two groups. The CFS group also had significantly higher LF/HF ratio (measure of frequency dependent HRV) during the speech and after the speech compared to the asthma group and the healthy controls.

The CFS group had significantly higher baseline scores on all 3 SCR measures when compared to the other two groups combined together. The CFS group showed

significantly higher SCR during preparation for the speech on the area under the curve SCR measure compared to the other two groups. The CFS group showed continued increase on SCR Max-Min during recovery, after the speech compared to a non-significant decrease in the other two groups.

These physiological differences are consistent with the hypothesis that adolescents with CFS may have differences in their autonomic responding to challenging situations. A fear of exercise as well as a slower recovery from a stressful situation seems particularly problematic in adolescent CFS.

Introduction

The Autonomic Nervous System

The autonomic nervous system (ANS) acts as a control system, working largely below the levels of consciousness (Gabella, 2001). The ANS affects heart rate, respiratory rate, salivation and perspiration amongst other bodily functions. Some of these will be investigated in this study. The ANS is classically divided into two subsystems; the parasympathetic nervous system (PNS) and the sympathetic nervous system (SNS). These systems operate independently in some functions and interact co-operatively in others (Janig, 1989).

The sympathetic division of the ANS aids in the control of the body's internal organs. This branch is often viewed as the 'fight or flight' system; vital in the body's response to stress (e.g. (Padget & Glaser, 2003)). The SNS is thought to counteract the PNS, which generally works to promote maintenance of the body at rest (Moore & Agur, 2007). The hypothalamus is a portion of the brain that directs a multitude of important functions in the body, with one of the most important functions being linking to the nervous system. The hypothalamus responds to signals of stress by recruiting the sympathetic division of the ANS (Miller & O'Callaghan, 2002).

Stress

A significant proportion of people with CFS report that their illness began with a prolonged period of stress. In the current thesis, 43.6% of adolescents with CFS reported that their illness began with a period of stress (chapter 3). There is indirect evidence that adolescents with CFS may be particularly sensitive to stress as they have

higher scores on measures of anxiety and social phobia (SCAS; (Crawley *et al.*, 2009)), vulnerability (Rangel *et al.*, 2000a) and anxiousness (Rangel *et al.*, 2003) compared to both healthy controls and illness controls (juvenile rheumatoid arthritis (Rangel *et al.*, 2003). However, the exact role of stress remains uncertain. There have been no previous experimental studies examining the physiological effects of stress on adolescents with CFS. This study examines the hypothesis that adolescents with CFS will experience increased physiological dysregulation when exposed to a stressful situation; a social performance task and instructions (anticipatory response) for an exercise task compared to healthy and illness (asthma) controls.

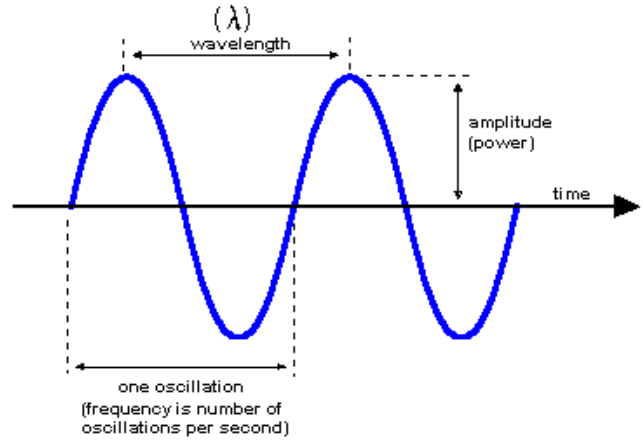
Physiological Measures

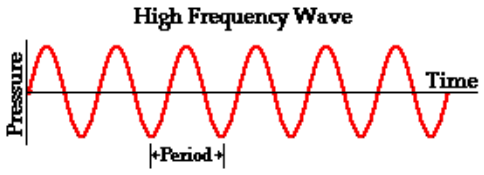
The parameters used to measure physiological dysregulation or a response to stress in this study were heart rate (HR), heart rate variability (HRV; both time and frequency domains) and skin conductance response (SCR; mean, MaxMin and integral). These are all described in full in the methods section of this chapter.

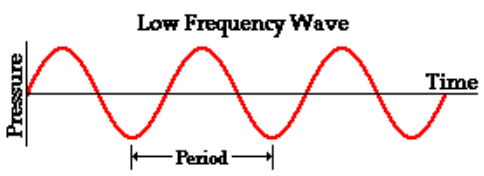
Heart rate variability is the beat to beat changes in HR frequency and a reliable non-invasive measure of activity of the ANS (Malik, 1996). HRV is important as lower HRV has been associated with physical health problems (Tsuji *et al.*, 1996). For example, lower HRV has been reported in adults with fibromyalgia (Cohen *et al.*, 2000), compared to healthy controls. Further, Kemp *et al.* (2012) reported decreased heart rate variability in adults with major depressive disorder and / or anxiety disorder compared to controls.

The frequency domain of HRV is measured using the LF/HF ratio. This is low frequency power / high frequency power. LF/HF ratio is an index of sympathetic modulation (a variation of system activity). Lower frequency is associated with the sympathetic nervous activity and high frequency power associated with the parasympathetic branch (Malliani *et al.*, 1994). A lower frequency is a smaller number of oscillations of waves per second and high frequency is more oscillations of waves per second. An increase in low frequency along with a decrease in high frequency is commonly observed in response to stress, resulting in an increase in LF/HR ratio. This is because the sympathetic branch (LF) responds during a stressful situation, i.e. fight or flight response (e.g. (Padget & Glaser, 2003)).

Figure 6.1: Waves to demonstrate high and low frequency power of a wavelength (Brockett, 2002)







The other aspect of HRV often measured is a time-domain parameter; the root mean of the successive differences (RMSSD). This is the square root of the mean of the sum of the squares of the successive differences between adjacent beat to beat intervals.

One would expect different outcomes in LF/HF ratio and RMSSD as they are measuring different aspects of HRV (e.g. (Sommerfeldt *et al.*, 2011; Wyller *et al.*, 2007b)). The time domain parameter (RMSSD) measures the magnitude of the temporal variations in the autonomically modulated cardiac rhythm. The frequency domain analysis provides the spectral composition of these variations. Higher LF/HF ratio and a lower RMSSD indicate a poor response to a situational demand (Malik, 2011).

Changes in skin conductance are related to changes in sweating which are, in turn, related to activity in the sympathetic branch of the autonomic nervous system (ANS). As sweat is an electrolyte solution, the more that the skin's sweat ducts and pores are filled with sweat, the more conductive the skin becomes (Figner & Murphy, 2011). Higher skin conductance indicates higher levels of sweat and higher levels of physiological dysregulation.

Background literature

Previous studies investigating CFS in adolescents - using very different experimental paradigms and objectives - have investigated some of these physiological parameters. Using a Head Up Tilt Task (e.g. (Galland *et al.*, 2008)), these authors have found higher HR, increased LF/HF ratio (e.g. (Sommerfeldt *et al.*, 2011)) and lower HRV at baseline as well as during task in comparison to healthy controls (e.g. (Wyller *et al.*, 2007a)). The head up tilt task is used as an investigative tool in the pathophysiology of

orthostatic stress (Brignole *et al.*, 2001). A participant is tilted between 60 - 80º and physiological measures are recorded.

Using a different orthostatic challenge test, a hand-grip task, (Wyller *et al.*, 2011; Wyller *et al.*, 2008) researchers found significantly higher heart rate and lowest heart rate variability responses in the adolescents with CFS compared to healthy controls leading to enhanced sympathetic predominance of heart rate control. One factor that may be contributing to these HR characteristics is a differential stress response in adolescents with CFS. No previous studies have investigated SCR in relation to stressful tasks in adolescents with CFS.

This study provides a novel contribution. It investigates physiological dysregulation in adolescents with CFS in response to a stressful task situation. It investigates possible differences in HR, HRV (RMSSD and LF/HF ratio) and SCR on two stressful tasks in adolescents with CFS compared to healthy adolescents and adolescents with asthma. HR and SCR were measured before and during a social performance task and during anticipation of an exercise task. Both tasks were designed to be challenging as performance was being assessed. In adolescents with CFS, an exercise task may be perceived as particularly demanding or threatening due to their fatigue and beliefs about fatigue (Richards *et al.*, 2005). This was an exploratory study, particularly focusing on the anticipation of stressful tasks and recovery from a stressful situation.

Hypotheses

1) HR will be significantly higher in the CFS group than the other two groups in anticipation of, during and after the Social Performance Task and in anticipation of the Exercise Task.

2) There will be significantly higher SCR (mean, MaxMin and integral) in the CFS participants compared to the other two groups associated with the anticipation and experience of the stressful tasks.

3) LF/HF ratio (frequency domain HRV) will be higher in the CFS group than in the other two groups, but RMSSD (time domain HRV) will be significantly lower in the CFS group than the other two groups on the two tasks. This is expected both at baseline and during the SPT.

Method

Study Design

This is a cross-sectional study where physiological parameters (HR and SCR) were continuously recorded for all participants during a number of potentially stressful time points (tasks). Three participant groups were compared; adolescents with CFS, adolescents with asthma and healthy controls.

Participants

Sixty-two adolescents with CFS, 31 adolescents with asthma and 78 healthy controls completed the tasks.

Missing Data

Table 6.1: Details of missing data in the physiological study

	Number of participants	Number Missing	Reason for missing data
CFS	62	4	1 GSR broke, 1 left at break, 2 refused
Healthy Control	78	4	2 no GSR device, 2 data unsuitable
Asthma	31	0	

Heart Rate, Heart Rate Variability and Skin Conductance Response

Continual measurements of HR, HRV and SCR were recorded using Powerlab 26T hardware and LabChart Pro Software (ADInstruments; www.adinstruments.com) run on a Toshiba laptop. This system is appropriate for a wide-range of research applications that require up to 4 input channels (this study used 2 channels). LabChart software is compatible with Windows and allows for data cleaning (e.g. filtering of noise in the HR window), data extraction and offline analysis. Measures of both HR and SCR are also visible on the laptop screen during live recording. PowerLab has been designed for use in psycho-physiological research (http://www.adinstruments.com/solutions/education/Psychophysiology/). Research studies have been published using this version of the PowerLab 26T (e.g. (Dixon *et al.*, 2010; Gaigg & Bowler, 2007; Kim *et al.*, 2008; Li & Chen, 2006; Westbury & Neumann, 2008)) to measure HR, HRV and SCR.

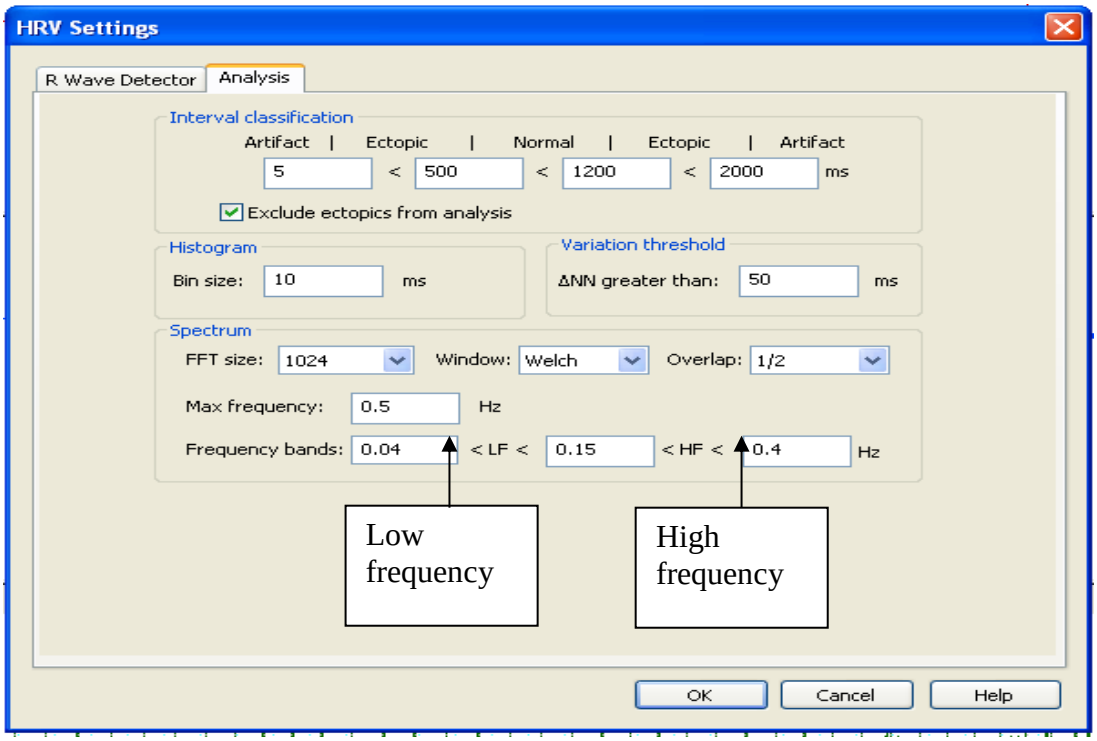
Throughout recording, visual markers were placed on the live recordings at each new 'stage' of the task. This allows easy identification of each section of physiological data; which part of the experimental procedure the data belongs to. This subsequently allows comparisons across groups during data analysis.

Heart Rate and Heart Rate Variability

For the pulsometer recording (used to measure HR and HRV), the pulse signal was sampled at 200mV to ensure optimum resolution for subsequent analyses. This sampling rate is considered the optimum sampling rate for HR and HRV in human subjects (AD Instruments). The Pulsometer was worn on the non-dominant middle-finger of the participant to record HR. This was recommended by the manufacturer as the participant was required to complete Visual Analogue Scales (VAS) during the task.

All settings for the HRV are outlined in figure 6.2. Intervals between successive heart beats were measured and frequency-domain parameters (LF/HF) were derived to calculate HRV as well as time-domain parameters (RMSSD). To identify normal beats (not ectopic or due to artefacts), the appropriate part of the cardiac cycle was first identified (the r-wave). Detection alogrithms in the LabChart 6 software enabled the identification of the r-waves in the signal. Manual editing was used to ensure correct identification of r-waves in instances of noise and fluctuations in the cardiac cycle.

Figure 6.2: HRV Settings in LabChart 26T

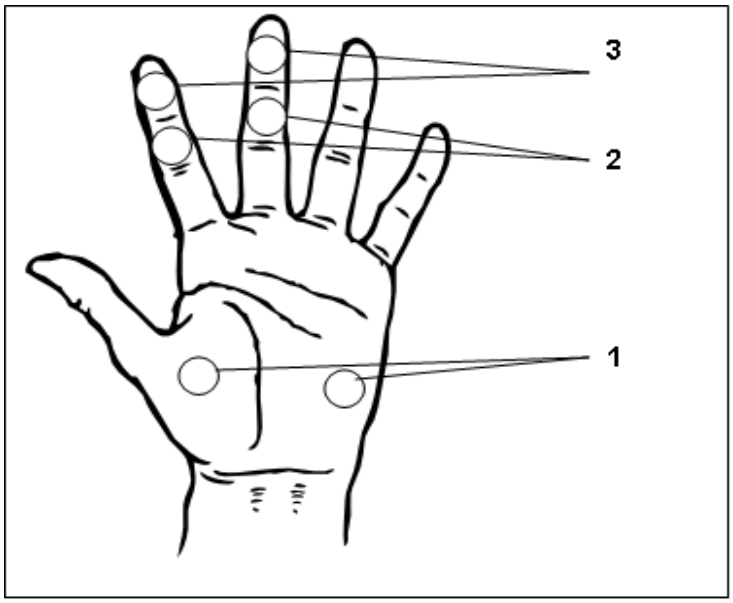


Once identified, r-waves were classified by an algorithm as normal, ectopic or as an artefact. A macro was written to extract the number of each of these variables to the datapad. The script was also manually scanned to ensure appropriate classification of beats, particularly in cases where participants had higher or lower than average heart rates. Following processing of the pulse signal, HRV was measured using the LF power / HF power which was also extracted for each time period and converted into numerical data using a macro. Here, there was a column for HF power, LF power and subsequently HRV. RMSSD was extracted for each time period and calculates the time-domain parameters of HRV.

Skin Conductance Response (SCR)

SCR was measured by passing a small electrical current across two electrodes placed on the skin. The methods used for measuring SCR vary in the precise location of electrodes attached to the palm of the hand. However the most common areas to place the electrodes are shown in figure 6.3; (1) the thenar and hypothenar eminences of the palms; (2) the volar surfaces on the medial phalanges; or (3) the volar surfaces of the distal phalanges.

Figure 6.3: Electrode Placements for SCR Recording (Dawson *et al.*, 2007)



In the current study, bipolar finger electrodes (each measuring 26mm x 20mm) with Velcro attachments were secured onto the finger of participants. These electrodes (compatible with the PowerLab data acquisition system) use a low, constant voltage AC excitation (22mVrms at 75 Hz) to allow enhanced safety and the use of dry electrodes, with no special electrodes or electrolyte needed. Measurement of absolute conductivity is up to 100microsiemens (µs). The current study recorded at 20 µs (40 µs maximum where necessary). This was determined specifically for each participant dependent on skin moisture levels. Dawson *et al.* (2007) recommend that a minimum response

amplitude of 0.05μs is used. This was employed as a cut-off in the current study, when data cleaning.

For this study, all participants washed their hands with soap and water before administration according to recommendations in the literature (e.g., (Venables & Christie, 1980; Walschburger, 1976), as cited in Boucsein (1992)). Participants washed their hands at the end of a break in the experimental session, supervised, then the electrodes and pulsometer were attached (see appendix 11 for session procedure, page 466).

In the current study, sites (2) were used (see figure 6.3). The ring finger was used instead of the middle finger as this was advised by the representative of the manufacturer and on the equipment training course. It avoids contact between the two electrodes. This allowed for the pulsometer to be placed on the 2nd finger, as recommended by the manufacturers. As advised, all jewellery was removed (Dawson *et al.*, 2007; Venables & Christie, 1973). Electrodes were attached to the non-dominant hand so that the dominant hand was free for any required tasks. All participants were asked to rest their hand on a pillow provided to make the experience comfortable.

There are 3 main aspects of SCR that can be measured. The first is the mean response (measured in μs). The second is the amplitude of the response (the difference in the selected SCR timeframe also called the Max-Min response). The final aspect of SCR is the integral (the area under the curve for the selected timeframe). This aspect is time-dependent. The mean SCR is most useful for comparing different time points between groups. The Max-min response is most appropriate when investigating an acute stimulus and the integral is used for specific time points. Given these differences, all 3 aspects of SCR are reported here.

Physiological Data Extraction

Data on SCR, HR and HRV were extracted from the raw physiological data recorded in the datapad of LabChart using the Powerlab 26T. The data was saved into blocks for task instruction and task completion, which are outlined below, (see figure 6.4 for a demonstration of the block recording):

1. Baseline

2. Instructions for Social Performance Task

3. Preparation for Social Performance Task

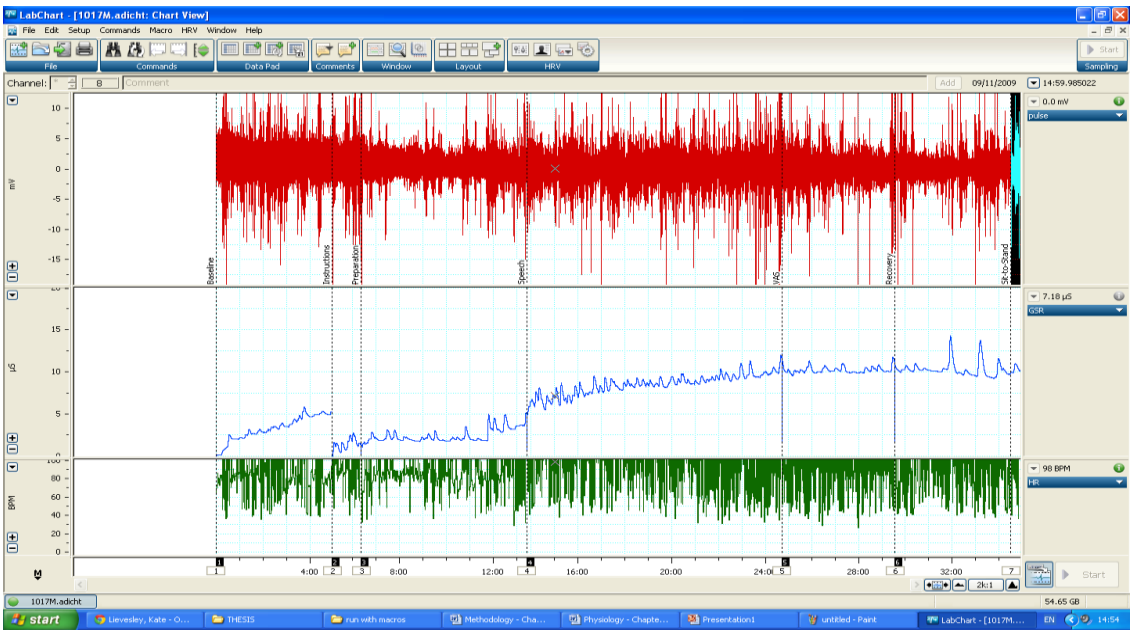
4. Social Performance Task

5. Visual Analogue Scales

6. Recovery

7. Instructions for Exercise Task

Figure 6.4: A screen shot to show the different blocks recorded



Macros were written with the assistance of the Labchart technical support team, following a one day training course on physiological data collection and analysis. Each participant has their own datapad file and this is transferred to SPSS for group comparisons. The following variables were extracted into the Labchart data pad for each of the blocks (as outlined above), saved as Excel files and transferred into SPSS for further analysis:

- SCR maximum minus minimum in the block (µs)
- SCR mean (µs)
- SCR integral (area under the curve)
- Mean heart rate (HR) in beats per minute
- Number of normal heart beats
- Number of eptopic heart beats
- Low Frequency Power (LF, ms^2)

- High Frequency Power (HF, ms^2)
- Heart rate variability (LF / HF ratio)*
- Heart rate variability (RMSSD)

**HF is an indicator of parasympathetic nervous system activation and LF is an indicator of sympathetic nervous system activation.*

Experimental Tasks (described in full in chapter 5, page 195)

Social Performance Task (SPT)

Participants were asked to give a 3 minute speech to the experimenter, which was videotaped. They were told that the experimenter would be evaluating their performance and that the video was being made to allow an evaluation of their performance by independent raters at a later point. The task elicits a level of stress that is manageable for the participants (Rapee & Lim, 1992). This task has been used before, and the same standardised procedure was used here as in the Rapee and Lim (1992) study investigating adolescents with social phobia.

Exercise Task (ET)

Five-repetition Sit-to-Stand Task (Csuka & McCarty, 1985)

A five-repetition sit-to-stand task was used to investigate physical functioning in the 3 groups. For the instructions of this task, participants were still connected to the physiological recording device. The equipment was then removed for the adolescents to complete the task. Participants were told they were being asked to rise to standing and return to sitting as quickly as possible, five times. Two trials were completed by all

participants. A record was made of the time taken to complete the task. This is widely used as a predictor of physical functioning (e.g. (Gill *et al.*, 1995)). This task and longer versions have been found to be acceptable in chronic illness in adults (Newcomer *et al.*, 1993). There is no reason to think that this short version is not acceptable in children. It is widely used as a clinical tool in CFS (e.g. Great Ormond Street Hospital CFS Service), but has not been researched in this population to date.

Procedure

Continual measurements of heart rate and skin conductance response were recorded through all elements of the social performance task and through the instructions for the exercise task. The task order is detailed in appendix 12 (page 468) in more detail, but for the purposes of this chapter, the social performance task was completed after a short break, split into the sections described above (page 247). After the recovery from the social performance task, participants were given the instructions for the exercise task.

Statistical Analyses

All analyses were completed using SPSS. All variables were explored for normality. Data was inspected visually using histograms, quantile-quantile (Q-Q) plots and box plots. This was also useful to identify any outliers. No serious violations of normality were identified for all variables (HR, HRV and SCR). The three groups were compared for scores on SCR mean, MaxMin and integral SCR, mean HR in beats per minute and heart rate variability (LF/HF ratio and RMSSD).

Repeated measures ANOVAs were used to investigate mean SCR, MaxMin SCR, HR and HRV variables over the 7 time points. This was either all points together or where applicable, during the specific stages relating to anticipation of a stressful event. Significant main effects and interactions were investigated further with paired t-tests or one-way ANOVAs as appropriate.

Because of the preliminary nature of this study, further exploratory analyses were conducted. Given the specific predictions that CFS would show a different response relating to anticipatory and actual stress, specific repeated measures ANOVAs were completed. These were for: preparation – speech, speech – recovery, and recovery from social performance task to exercise task instructions. An ANCOVA was used where it was deemed necessary to control for a baseline score. Post-hoc analyses were conducted and reported when there were between group differences.

Results

Time of day for task session completion

Table 6.2: Time of day participants completed the task session

	AM	**PM**
CFS	31%	69%
Asthma	32%	68%
Healthy Control	41%	59%

The majority of participants in each group completed the tasks during the afternoon. This was recommended where possible for the cortisol sampling (chapter 7).

Baseline Scores

Table 6.3: Baseline scores for all groups on physiological variables; means, standard deviations and results of the one-way ANOVAs

Physiological Parameters	CFS (N=58)	Asthma (N=31)	Healthy Controls (N=74)	Result (one-way ANOVA)
Min-Max SCR	10.14 (6.05)	7.93 (4.00)	8.35 (6.21)	F(2,159) = 2.064, p = .130
Mean SCR	4.99 (4.53)	4.06 (2.09)	3.56 (3.35)	F(2,159) = 2.504, p = .085
Integral SCR	1694.53 (1146.42)	1203.36 (609.28)	1331.17 (1146.00)	F(2,158) = 2.746, p = .067
Mean HR	82.53 (9.90)	80.23 (9.57)	79.88 (7.54)	F(2,155) = 1.490, p = .229
LF/HF ratio	1.98 (0.98)	2.14 (1.37)	1.87 (1.29)	F(2,155) = .556, p = .574
RMSSD	49.72 (20.28)	61.16 (20.34)	63.55 (35.06)	F(2,157) = 4.00, p = .020*

Baseline means for each of the physiological variables are recorded in table 6.3. There was a significant difference on RMSSD (HRV). The CFS group had a significantly lower HRV than the other 2 groups at baseline. The other variables did not reach statistical significance.

Given the hypothesis that the CFS group would show significant differences on these measures compared to both control groups, it was considered justified to combine the 2 control groups to conduct planned comparisons. Once combined, the CFS group had significantly higher scores of SCR in all 3 aspects and the significantly lower HRV remained (all t's larger than 2.01). Mean HR was not quite significant (t = 1.722, p = .087).

Skin Conductance Response - Analysis of mean SCR over time (µs)

Exploratory analyses (see figure 6.5 and table 6.4) indicated significant within-subjects effects of time for two of the analyses but no other significant effects. Paired t-tests revealed that from the 'preparation for speech to the actual speech' and again for 'recovery from speech to instructions for exercise task' there was a significant increase in mean SCR when analysing all groups together.

Figure 6.5: SCR (mean) at all seven time points for the 3 groups

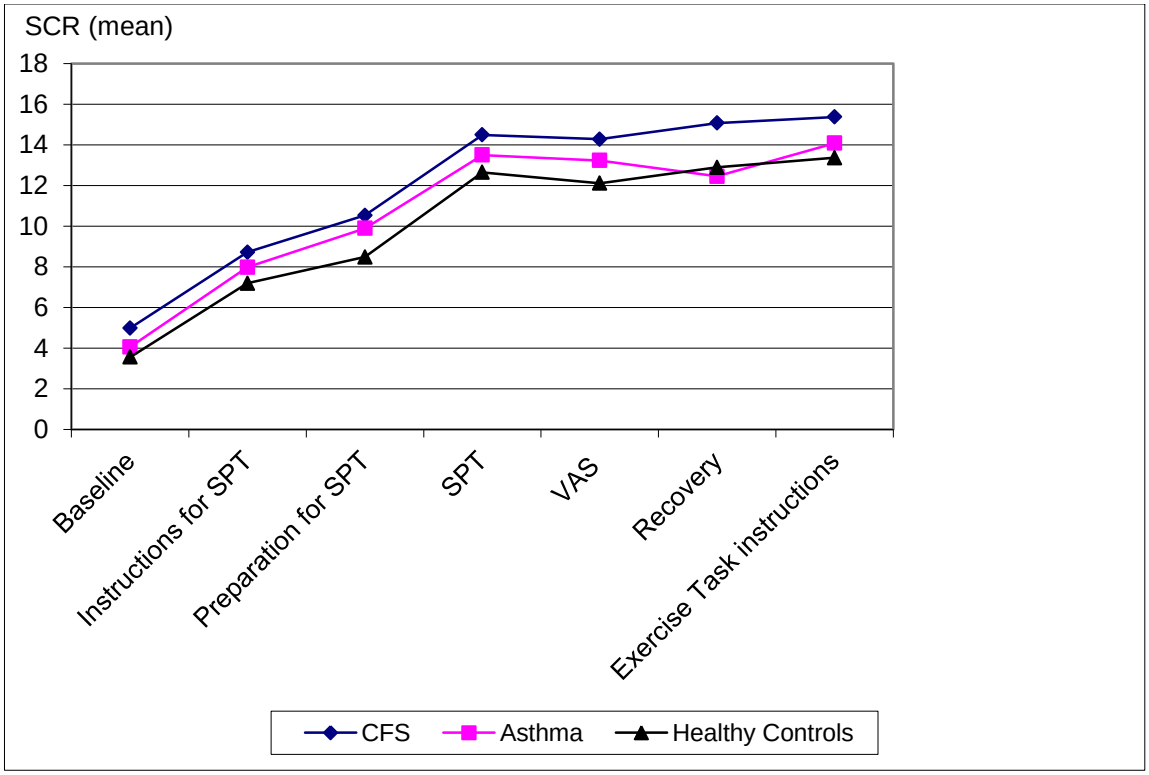


Table 6.4: Stages relating to anticipation / recovery of a stressful event (SCR Mean); repeated measures ANOVAs

Preparation for speech – speech	**Speech – recovery**	**Recovery from speech – instructions for exercise task**
Within subjects: F(1,159) = 168.08, p = .000* Group interaction: F(2,159) = .283, p = .754 Between subjects: F(2,159) = 1.007, p = .368	Within subjects: F(1,155) = .398, p = .529 Group interaction: F(2,155) = 1.124, p = .328 Between subjects: F(2,155) = .812, p = .446	Within subjects: F(1,153) = 14.74, P = .000* Group interaction: F(2,153) = .927, p = .398 Between subjects: F(2,153) = .684, p = .506

Skin Conductance Response – Maximum minus minimum (µs)

The Repeated Measures ANOVA for SCR (Max-Min) found only a significant within groups' effect, with all groups SCR increasing over time and starting to reduce again after a recovery period (see figure 6.6). There was a significant increase from 'instructions to preparation', 'preparation for speech and speech to recovery'. There was a significant decrease from 'speech to instructions for sit to stand task'. The Max-Min was significantly higher at all subsequent time points compared to baseline. Even though the Max-Min curve was declining by the exercise task, it was still significantly higher than at baseline.

These results are shown in the exploratory analysis investigating change between key time-points and are shown in table 6.5. Only one stage showed a group by time interaction: the change in SCR (Max-Min) from 'speech to recovery stage'. Paired t-tests indicated that the CFS group showed a significant increase in SCR (Max-Min) between those two stages while the other two groups showed no significant change. One-way ANOVAs revealed no significant difference between groups at either of the two time points. All 3 exploratory repeated measures ANOVAs revealed a within subjects effect. From 'preparation for speech to the speech' itself, there was a significant increase across groups. For 'recovery from speech to exercise task instructions', the participants showed a significant decrease in SCR (max-min).

Figure 6.6: SCR (max-min) at all seven time points for the 3 groups

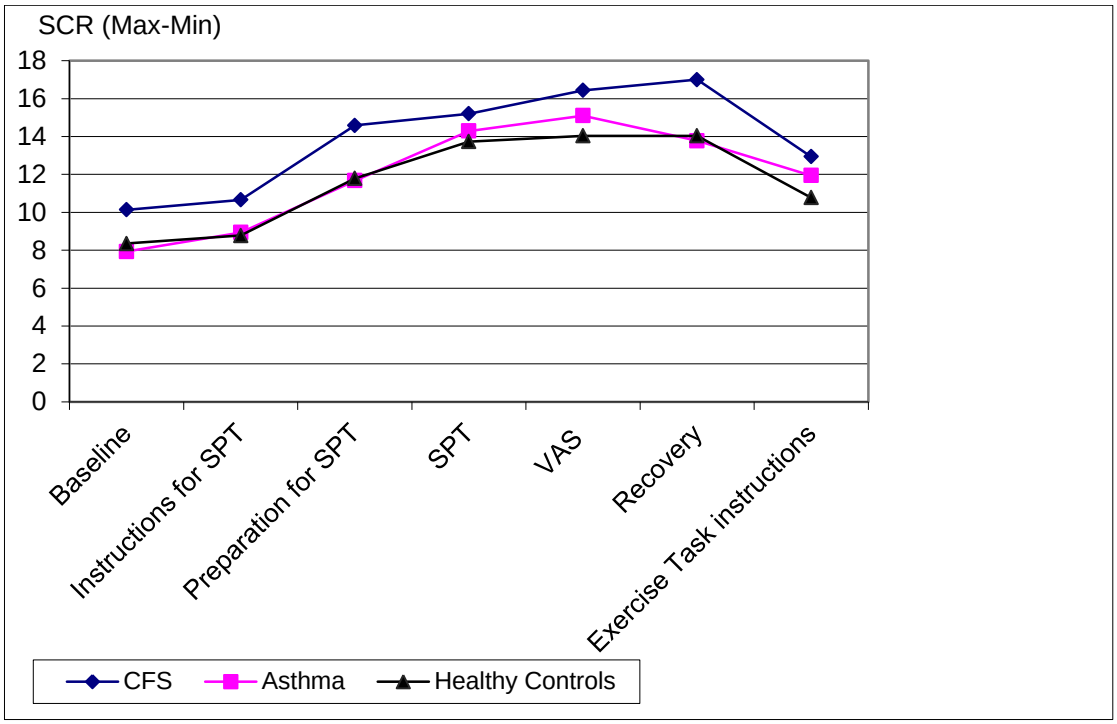


Table 6.5: Results of repeated measures ANOVA investigating change in SCR (max-min) between different stages

Preparation for speech – speech	**Speech – recovery**	**Recovery from speech – instructions for exercise task**
Within subjects: F(1,160) = 25.975, p = .000* Group interaction: F(2,160) = 2.949, p = .055 Between subjects: F(2,160) = .247, p = .247	Within subjects: F(1,157) = 5.832, P = .017* Group interaction: F(2,157) = 3.898, p = .022* Between subjects: F(2,157) = 1.271, p = .283	Within subjects: F(1,154) = 24.856, p = .000* Group interaction: F(2,154) = .286, p = .752 Between subjects: F(2,154) = 1.255, p = .294

Skin Conductance Response – Integral (area under the curve)

For the area under the curve, it is not appropriate to conduct a repeated-measure ANOVA as each of the sections is a different length to that before it. Instead, a one way ANOVA was conducted for each time point to investigate between group differences (table 6.6). The VAS section is not included in the analyses as this section is strongly affected by time taken to complete the VAS. The ANOVAs showed that there were

significant group differences in SCR integral in preparation for the SPT. At the preparation for SPT stage, the CFS group had significantly higher scores than the healthy control group (p = .015) only.

Table 6.6: One-way ANOVA findings, Means and Standard Deviations for Mean Skin Conductance Response – integral (area under the curve) for all groups

Skin Conductance Response – integral (area under the curve)	**Group**			
	CFS (N=58)	**Asthma (N = 31)**	**Healthy Controls (N = 74)**	**Results**
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	
Baseline	1694.53 (1146.42)	1203.36 (609.30)	1331.165 (1146.00)	F(2, 158) = 2.746, p = .067
Instructions to SPT	754.90 (636.69)	805.24 (519.20)	668.77 (681.20)	F(2, 159) = 0.596, p = .552
Preparation for SPT	3716.39 (3475.67)	2535.82 (1622.46)	2495.92 (1702.76)	F(2, 159) = 4.440, p = .013*
SPT	2617.44 (2028.44)	2256.43 (1577.92)	2691.66 (2195.69)	F(2, 159) = 0.514, p = .599
Recovery from SPT	4582.17 (3608.57)	3030.52 (2770.33)	3795.44 (2733.75)	F(2, 157) = 2.522, p = .084
Instructions for ET	261.94 (279.66)	268.456 (231.64)	240.36 (226.10)	F(2, 157) = 0.188, p = .829

Heart Rate (HR; Beats per Minute)

Analysis of HR over time

A repeated measure ANOVA for mean HR revealed only a significant within-subjects effect of time (see figure 6.7). Paired t-tests indicated that HR was significantly higher than baseline during the instructions for both the speech task and the exercise task, as well as during the speech itself. There was not a significant increase from baseline to preparation or baseline to recovery. There was not a significant difference between the speech and the instructions for the exercise task (p=.940).

Results of repeated measures ANOVAs for changes in HR between specific time-points are shown in table 6.7. The RM ANOVA for 'preparation to speech' revealed a group by time interaction. Paired t-tests indicated that the healthy control group was the only group to significantly increase in HR from preparation to speech. A one-way ANOVA indicated that the CFS group had a significantly higher HR at preparation, but there were no significant group differences during the speech.

There was another group by time interaction from 'speech to recovery'. A one-way ANOVA indicated that the CFS group had a significantly higher HR at recovery than the other two groups. The healthy control group was the only group to significantly decrease in HR from speech to recovery. Finally, there was a significant between group effect between 'recovery and instructions for the exercise task'. Over these two final time-points, the CFS group had higher HR than the healthy controls, even when controlling for baseline HR.

Figure 6.7: HR at all seven time points for the 3 groups

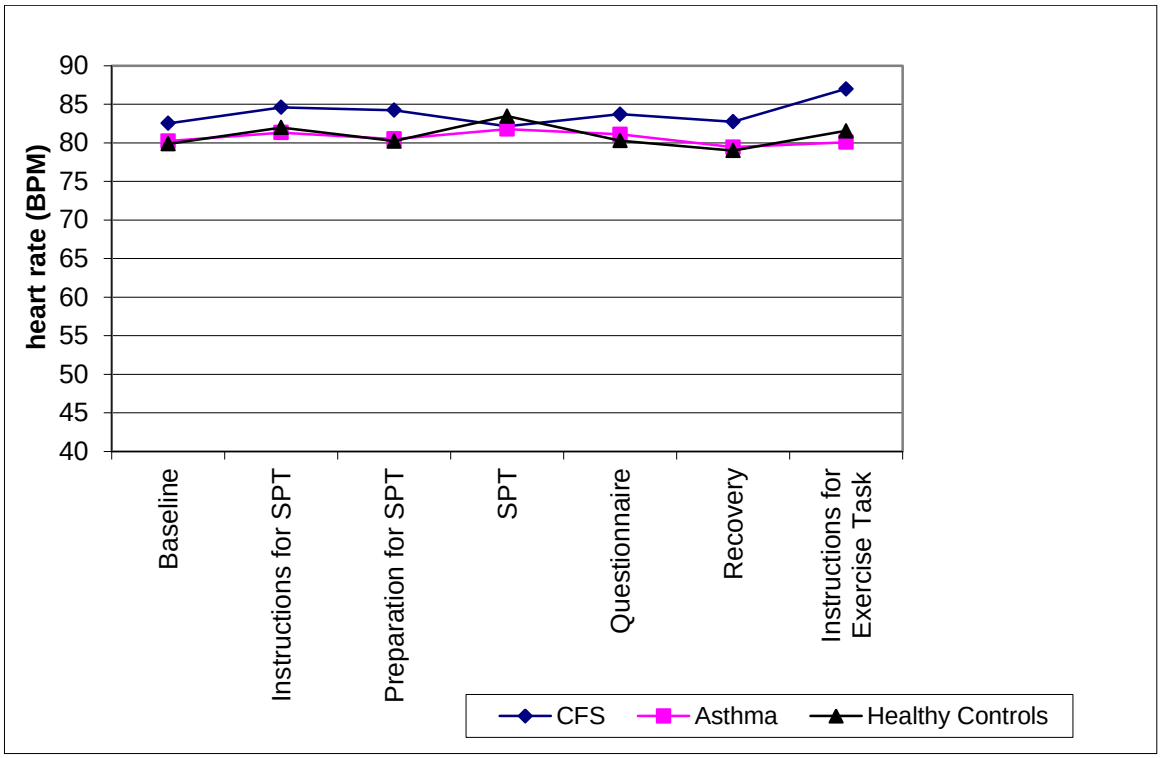


Table 6.7: Results of repeated measures ANOVAs comparing change in mean heart rate between stages relating to anticipation / recovery of a speech task

Preparation for speech – speech	**Speech - recovery**	**Recovery from speech – instructions for exercise task**
Within subjects: F(1,149) = 2.770, p = .098 Group interaction: F(2,149) = 5.59, p = .005* Between groups: F(2,149) = .660, p = .518	Within subjects: F(1,144) = 14.881, p = .000* Group interaction: F(2,144) = 3.517, p = .032* Between groups: F(2,142) = .475, p = .623	Within subjects: F(1,142) = 11.024 p = .001* Group interaction: F(2,142) = .908, p = .406 Between groups: F(2,142) = 3.613, p = .029*

Heart Rate Variability (LF / HF ratio, ms²)

Analysis of LF/HF ratio over time

The RM ANOVA for LF/HF ratio showed a significant between-subjects effect (see figure 6.8). Post-hoc tests revealed that the CFS group had significantly higher LF/HF ratio than the healthy controls for the session as a whole. There were no significant

differences between the CFS group and asthma group or the asthma group and the healthy controls.

A repeated measures ANOVA for specific points (table 6.8) of anticipation / recovery from the social performance task revealed a between group difference from 'preparation for speech to speech'. Post-hoc tests showed that the CFS group were significantly higher than the healthy controls only. From 'speech to recovery', the same pattern of group differences was found.

Figure 6.8: Heart rate variability (HF/LF ratio) for all groups across each of the seven time points

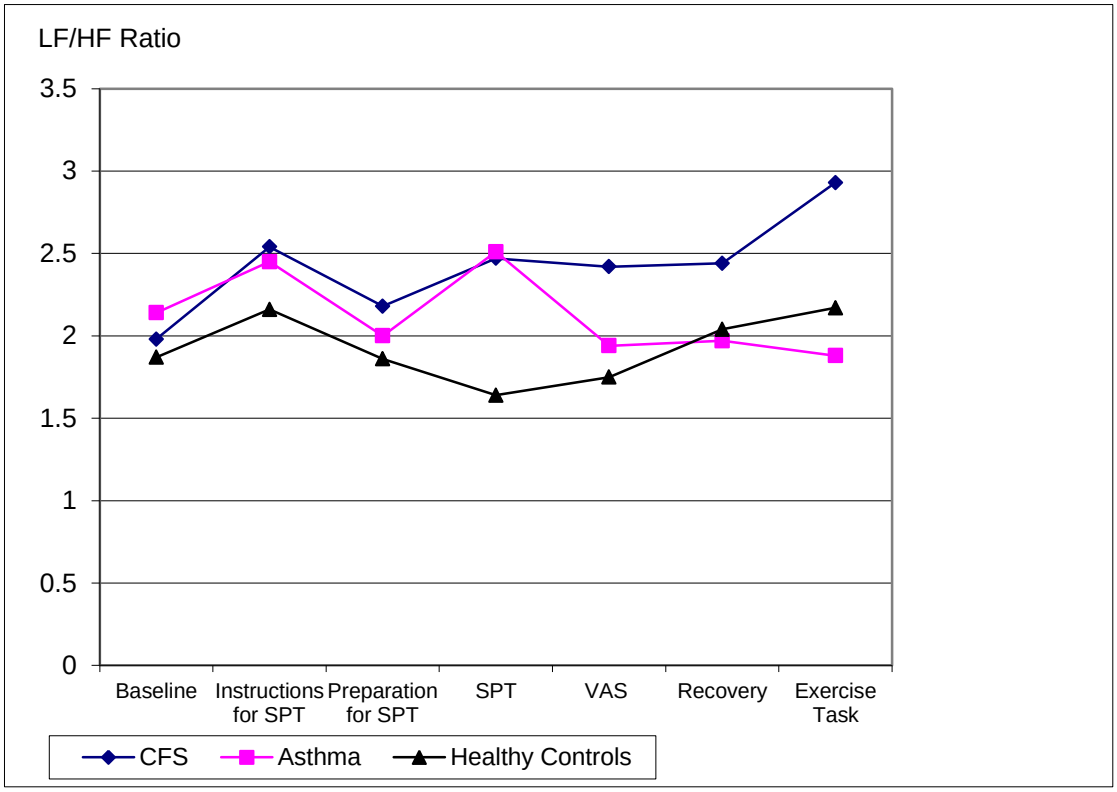


Table 6.8: Results of repeated measures ANOVAs comparing change in Heart rate variability (LF/HF ratio) between stages relating to anticipation / recovery of a speech task

Preparation for speech – speech	**Speech - recovery**	**Recovery from speech – instructions for exercise task**
Within subjects: F(1,133) = 2.146, p = .145 Group interaction: F(2,133) = 1.67, p = .192 Between subjects: F(2,133) = 5.22, p = .007*	Within subjects: F(1,126) = .092, p = .762 Group interaction: F(2,126) = 3.001, p = .053 Between subjects: F(2,126) = 3.789, p = .025*	Within subjects: F(1,113) = .684, p = .410 Group interaction: F(2,113) = .465, p = .629 Between subjects: F(2,113) = 2.686, p = .072

HRV (RMSSD; time domain parameter)

The repeated measures ANOVA for HRV (RMSSD) for all time points revealed no significant main effects or interactions (table 6.9). Planned exploratory analyses were conducted for the stages connected to anticipatory response or recovery. There was a significant within-subjects effect for 'preparation for speech to speech', with participants increasing in HRV between those time-points.

Figure 6.9: The root mean of successive differences (HRV) over time for all groups

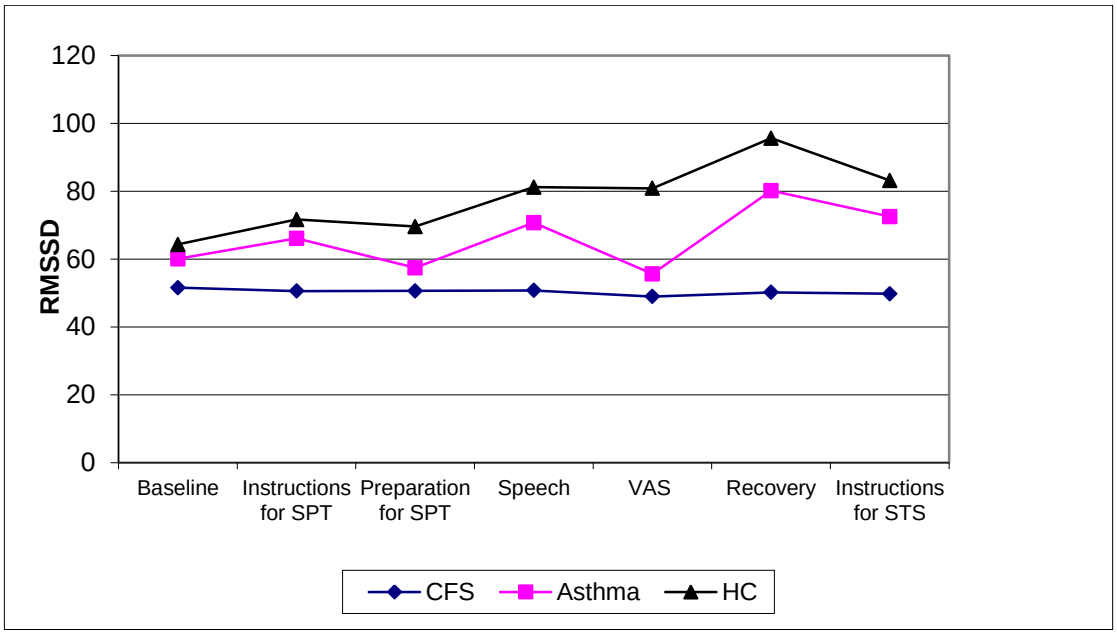


Table 6.9: Results of repeated measures ANOVAs comparing change in RMSSD between stages relating to anticipation / recovery of a speech task

Preparation for speech – speech	**Speech - recovery**	**Recovery from speech – instructions for exercise task**
F(1,136) = 7.641, p = .006*	F(1,130) = 1.769, p = .186	F(1,117) = 2.490, p = .117
F(2,136) = .377, p = .686	F(2,130) = .532, p = .589	F(2,117) = .700, p = .499
F(2,136) = 1.976, p = .143	F(2,130) = 2.258, p = .109	F(2,117) = 2.417, p = .094

Correlations between physiology and self-report measures

Correlation analyses were conducted for self-report measures and physiology recordings. There were no significant correlations between the subjective ratings of anxiety and physiological dysregulation in terms of either heart rate or skin conductance at different time points.

Discussion

Main findings

Baseline scores of physiological variables

At baseline, the CFS group had a significantly lower baseline HRV (RMSSD) than the other groups. This could be very important as low HRV is a sign of poor physical health (Tsuji *et al.*, 1996). Previous research has found that lower HRV is observed in fibromyalgia (Cohen *et al.*, 2000), as well as depression and anxiety (Kemp *et al.*, 2012). In addition, lower HRV was also reported in adolescents with CFS (Wyller *et al.*, 2007a) compared to healthy controls.

Given that the situation of coming to the hospital may have been stressful in itself, it is not possible to ascertain from this study whether the lower HRV at baseline represents a chronically lower HRV or an abnormal response to the stress of the clinic visit. Future research could investigate whether the same results are found if the physiological measures are taken in different situations, such as the young person's home environment.

In contrast to the group difference in baseline HRV as measured by the RMSSD, the LF/HF ratio was not significantly different between the groups. Where baseline HRV is lower, one may have expected the LF/HF ratio to be significantly higher. However, they are two different aspects of heart rate variability to measure the stress response, so it isn't a guarantee that they will result in exactly the same findings. The CFS group did have a significantly higher LF/HF ratio over time highlighting the stress response in this population.

Given the hypothesis that the CFS group would have different physiological responses to the other groups, it was considered justified to combine the 2 control groups to conduct further planned comparisons. Once combined, the CFS group had significantly higher scores on all 3 aspects of baseline SCR. This is the first time that SCR has been investigated in adolescents (or adults) with CFS. However, higher baseline SCR has been reported in adults with panic disorder (Roth *et al.*, 1990). High baseline SCR indicates higher levels of arousal which may have been induced by a feeling of being stressed. This corresponds with the findings in this study.

Skin Conductance Response

This study is the first to investigate SCR in response to a stressful situation in adolescents with CFS. The key finding was that the CFS group showed a significantly higher SCR in anticipation to the speech task than the other two groups, using the SCR integral (area under the curve) measure. This indicates greater physiological dysregulation in the CFS group than the other two groups when faced with a stressful situation, mirroring the self-report anxiety VAS in the previous chapter (chapter 5). Furthermore, on the SCR (Max-Min) measure, the CFS group showed a significant increase between the speech and recovery phase, while the other two groups showed a non-significant decrease. A slower physiological recovery after a stressful situation, also known as 'response stereotypy has been shown in chronic anxiety (Malmo *et al.*, 1950) when patients were exposed to a startle stimulus and took much longer to return to normal than the healthy controls. These authors suggest this slowness of recovery reflects homeostatic abnormality. Although a different experimental paradigm, a similar finding emerged in this study. This slowness of recovery was also observed in the Roth

et al. (1990) study investigating adults with panic disorder – 'higher and more slowly declining SCR'.

Prolonged activation and stress theory includes slow recovery from stressors with a suggestion that prolonged physiological activity (times of stress) may result in a somatic condition (Krantz & McCeney, 2002). This could suggest the slower recovery observed in this study indicates a prolonged experience of stress in the CFS group. It is too early to draw conclusions on this finding given it is the first SCR investigation, but it could be important in understanding CFS in adolescents. There has been a suggestion that such differences in physiological responding in conditions of stress may highlight a pre-existing risk factor for CFS that needs further investigation; sustained arousal may cause fatigue (Wyller *et al.*, 2009).

There were no other group differences or interactions for SCR. For the CFS group mean SCR and SCR Max-Min were consistently higher than the other two groups. With a larger sample size these differences might have reached statistical significance. In general the sample showed there was a typical stress response to the tasks, with mean SCR and max-min SCR increasing over time, particularly around the tasks with the CFS group recovering more slowly.

Heart Rate

The within-subjects effect and subsequent paired t-tests revealed that HR was significantly higher than baseline during the instructions for both the speech task and the exercise task as well as during the speech itself. This reveals an anticipatory response across all groups to a stressful situation as well as experience of physiological

dysregulation during the completion of the stressful task (speech). As predicted, the CFS group had a significantly higher HR in anticipation of both of the two stressful tasks than the other two groups. This suggests that the CFS group are more physiologically aroused by the tasks than the other two groups; apprehensive about their ability to complete it perhaps. However, the correlation analyses revealed no significant relationships between the subjective ratings of anxiety, heart rate, sweaty hands and other physiological dysregulation indicators and heart rate before, during or after the task. Surprisingly, only the healthy control group showed a significant increase in HR between the speech preparation and speech itself. The CFS group had significantly higher HR during the recovery stage than the other two groups, indicating a lower physiological recovery after a stressful event. The healthy controls were the only group to show a significant decrease in HR from speech to recovery.

SCR and HR data revealed a slower recovery in the CFS group than the other two groups after the speech task. Possible reasons for slow recovery in HR after a stressful task have to date mainly focused on exercise as the stressor and report a lack of physical activity and poor lifestyle as key (Lauer, 2001).

Within CFS specifically, there are many possible causes of these physiological differences, including stress or changes in activity or other health behaviours associated with the condition. It is also possible that their slow recovery is linked to their psychological characteristics e.g. their lower expectations and perceived performance on the task compared to the other groups as observed in chapter 5. It is possible that they were ruminating about their performance afterwards more than the other groups. These current findings of HR differences in the CFS group are in line with the previous literature that has found higher HR in CFS patients compared to healthy controls using the head-up tilt test (Galland *et al.*, 2008) or the hand-grip task (Wyller *et al.*, 2011).

Seemingly, similar findings relating to HR emerge from different experimental paradigms. One of the reasons for the previously reported HR differences in adolescents with CFS compared to healthy individuals may be due to differences in their autonomic responding in challenging situations, in particular exercise. This study found an increase in the HR of adolescents with CFS when they were told they would be completing an exercise task. It is possible that in the previous studies involving the HUT, participants may have perceived or experienced this to be challenging or stressful, and this stress could have influenced their HR responding.

Heart rate variability

LF/HF ratio

The CFS group had significantly higher heart rate variability as measured by the LF / HF ratio than the healthy controls on the physiological task as a whole. The CFS group were not significantly different from the asthma control group on this measure.

LF/HF ratio over time has been found to be higher in adolescents with CFS (Sommerfeldt *et al.*, 2011) as well as other chronic illnesses such as postural orthostatic tachycardia syndrome (POTS; (Stewart, 2000)). This frequency-domain parameter as described earlier in this chapter is used to indicate balance between sympathetic and parasympathetic tone – which can indicate autonomic balance (i.e. a poor co-ordination between these two systems). This higher level in the CFS group indicates the higher sympathetic response (i.e. low frequency) compared to a parasympathic response. This sympathetic dominance may indicate 'burn out' due to stress which has been considered possible in patients with CFS. Cognitive behavioural models have suggested that a "boom and bust" approach to life, which is characteristic of people with CFS (e.g.

(Surarwy *et al.*, 1995)). Activity becomes symptom dependent and as time goes on, the symptoms become more and more controlling. This fluctuation in activity levels is addressed in cognitive behavioural therapy (Chalder *et al.*, 2002) with patients encouraged and supported in developing a consistent routine to avoid this 'boom and bust' approach to activity.

Root mean of successive differences (time domain HRV)

For the other measure of heart rate variability, the root mean of successive differences (RMSSD), there were no group differences, apart from the already discussed baseline RMSSD. This was significantly lower in the CFS group. It is surprising that the RMSSD did not reach significant group differences. The response appears consistently lower than the other groups and more importantly flattened throughout. Perhaps if the numbers were larger, these differences would have reached significance.

Clearly these physiological parameters demand further investigation in adolescents with CFS, across different paradigms. Seemingly, adolescents with CFS do have an altered cardiovascular and autonomic response to stress compared with healthy controls in particular. There is preliminary evidence that these differences in cardiovascular response normalise over time but there was no indication that these improvements correlated with self-reported improvements in symptoms or functioning (Sulheim *et al.*, 2012).

Limitations of the Study

There are some limitations to the psycho-physiological recordings. Although the same room was used for experimental testing for all CFS patients, the healthy control participants and asthma participants were primarily seen in schools or local surgeries respectively. It was therefore not possible to ensure that the temperature of the room was the same. This may have influenced the physiological outcomes to some degree, but this is considered to be minimal. Further, the participants were not all tested at the same time of day, which may influence the outcomes. However, the time of day was always recorded and the groups were matched as closely as possible for time of testing. The majority of each group were seen in the afternoon.

A pulsometer was used on the adolescents rather than the ECG stickers often used on participants' chest. This was thought to be less invasive for these adolescent participants. However, there were times when completing the tasks (e.g. the speech or the VAS) that the amount of noise increased on the physiological recordings due to movement. This was similar across all 3 groups.

As discussed in the method section, the methods for SCR recording vary. Some authors recommend the use of Ag/AgCl surface electrodes filled with isotonic electrolytic paste (e.g. (Venables & Christie, 1980)) as they suggest it gives a more sensitive reading. However, the current equipment used dry surface electrodes for the same purpose and therefore isotonic electrolytic gel was not required (e.g. (Dixon *et al.*, 2010; Li & Chen, 2006)).

Chapter Summary

The main findings were that the CFS group had a significantly lower HRV at baseline and throughout the experimental tasks. This may indicate poor physiological response to a stressful situation. HR was significantly higher in the CFS group in anticipation of an event as well as during recovery. In conjunction with a generally higher SCR, adolescents with CFS seem to exhibit differences in their autonomic responding in challenging situations. Anticipation of exercise as well as a slower recovery from a stressful situation seems to be particularly problematic. This may relate to higher levels of fatigue and anxiety, where they are more anxious about completing stressful tasks. It is also possible that having an illness such as CFS, characterised by multiple physical symptoms and associated with an inability to perform on a variety of tasks, leads adolescents to feel more anxious about performance related tasks. The next chapter will address cortisol levels in the groups during the experimental tasks to continue the investigation of physiological responses.

Chapter 7: Salivary cortisol response to a social performance task; area under the curve

Synopsis

Evidence is emerging with regard to reduced cortisol output in patients with CFS (Roberts *et al.*, 2004). Adolescents with CFS were compared with healthy controls and adolescents with asthma in salivary cortisol output surrounding a social performance task. Gender, medication use, anxiety and depression were taken into account. Associations between cortisol output and clinical measures were examined.

Salivary cortisol was measured at baseline (at arrival to the task session), a second baseline after the task session break, 1 minute before the social performance task as well as 10, 20 and 30 minutes afterwards. There were 54 CFS patients, 26 asthma patients and 69 healthy controls in the study. Cortisol output was measured by calculating the area under the curve (AUC), with respect to increase (AUC_I) and with respect to the ground (AUC_G). It was hypothesised that under the stress of being asked to give a brief presentation, adolescents with CFS would show disturbed cortisol responses compared to the other two groups, with CFS having lower cortisol output.

In female participants, there was a significantly lower AUC_I than the male participants, suggesting that females have lower change over time generally, indicating a less sensitive HPA system (flattened cortisol response). Further analyses were conducted but no other significant findings emerged. It is clear that many gaps remain. Any conclusions must still be treated with caution at this point.

Introduction

As has already been recognised in this thesis, CFS is likely to be a multi-factorial condition in which several factors (e.g. psychological, biological and social) interact. Within the biological domain, much remains unclear. Evidence is emerging with regard to reduced cortisol output in patients with CFS (Roberts *et al.*, 2004). This may be a primary aetiological factor of CFS or an association of other correlates associated with the condition, such as increased stress. In this study, salivary cortisol will be measured. It is considered a non-invasive method of assessing the HPA axis function in response to a stressful situation.

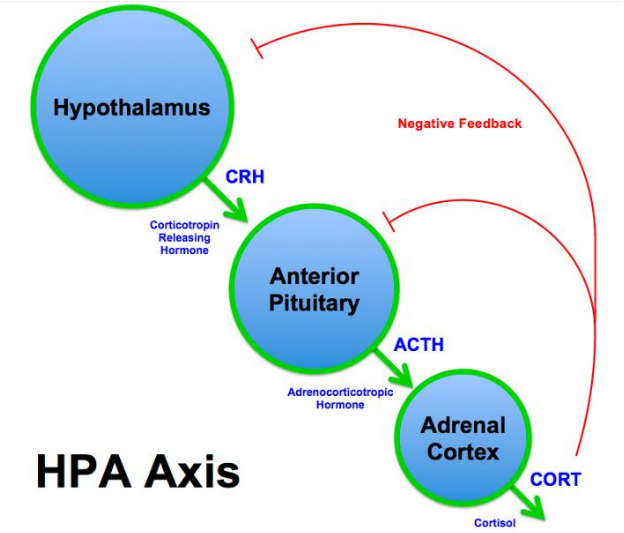
Hypothalamic Pituitary Adrenal (HPA) axis

The HPA axis is a complex set of direct influences and feedback interactions among the hypothalamus, the pituitary gland, and the adrenal glands (which are located on top of the kidneys) (Reichlin, 1998). The axis is a major part of the neuroendocrine system that controls reactions to stress and regulates many bodily processes, including digestion, the immune system, as well as mood and emotions (Cleare, 2003). The physiological role of the HPA axis is fundamental to the body's stress response.

The key elements of the HPA axis are the para-ventricular nucleus of the hypothalamus, which contains neuroendocrine neurons that synthesise and secrete vasopressin and corticotrophin-releasing hormone (CRH). These two peptides regulate the anterior lobe of the pituitary gland (Reichlin, 1998). In particular, CRH stimulates the secretion of adrenocorticotropic hormone (ACTH). In turn, ACTH acts on the adrenal cortex, which produces glucocorticoid hormones (mainly cortisol) in response to stimulation by

ACTH. Glucocorticoids in turn act back on the hypothalamus and pituitary gland in a negative feedback cycle. This is shown in figure 7.1.

Figure 7.1: A basic HPA axis summary (Sweis, 2012)



Release of CRH from the hypothalamus is influenced by stress, physical activity, illness, blood levels of cortisol and by the sleep / wake cycle (circadian rhythm) (Cleare, 2003). In healthy individuals, cortisol rises rapidly after wakening, reaching a peak within 30-45 minutes. It then gradually falls over the day, rising again in late afternoon. Cortisol levels then fall in late evening, reaching a trough during the middle of the night. An abnormally flattened circardian cortisol cycle has been linked with CFS (MacHale *et al.*, 1998). Researchers have also started to investigate the Hypothalamic Pituitary Adrenal (HPA) axis function in adolescents with CFS (Segal *et al.*, 2005).

Background literature

Conditions of low circulating cortisol are characterised by marked fatigue and debility which later led to suggestions that CFS was mediated by low circulating cortisol levels

(e.g. (Demitrack *et al.*, 1991)). Indeed, one of the few biological changes in CFS that has been reliably demonstrated is a reduced cortisol output (Papadopolous & Cleare, 2012). Hypocortisolism is commonly described in adults with CFS over the day (Cleare, 2003) as well as in response to awakening (Roberts *et al.*, 2004) which has been used as a non-invasive way of measuring the cortisol response to stress. Stress is reported by some patients with CFS as a contributory factor to their condition. Research in adults has suggested that those individuals who have been chronically stressed (for example exposed to childhood trauma) are likely to show lower levels of cortisol; a blunted cortisol awakening profile (e.g. (Heim *et al.*, 2009)). Heim *et al.* (2009) highlighted childhood trauma as a risk factor of CFS, where the early life experiences trigger physiological changes in the patient, consequently resulting in symptoms of fatigue. They reported that individuals with CFS who had experienced childhood trauma had flattened cortisol awakening response profiles compared with well control participants (Heim *et al.*, 2009). Although not looking at childhood trauma, instead inducing a stressful response, the cortisol response profile is of great interest in this study. The idea that hypocortisolism may be a pre-existing risk factor for CFS is well in line with the potential physiological effects of decreased cortisol availability under conditions of stress.

A case-control study (Segal *et al.*, 2005) reported adolescents with CFS (N=23) had significantly lower mean cortisol levels than age matched controls (N=17) in response to a low dose synacthen test (LDST). Kavelaars *et al.* (2000) found no differences in baseline or corticotrophin releasing hormone (CRH) induced cortisol between 15 CFS patients and healthy controls, but baseline adrenaline levels were significantly higher in CFS patients. Wyller *et al.* (2010) found that serum cortisol concentrations in 67 adolescents (12-18 year olds) with CFS were only slightly and non-significantly lower

than levels in 55 healthy control adolescents. They measured the serum concentrations from blood samples between 8 and 9am in all participants. These studies all used a blood sample to assess HPA axis function. Salivary cortisol is much less invasive and easier to measure at several time points. This is recommended as cortisol is a hormone showing diurnal variation so more than one time point would be more reliable (Nicolson, 2008). Salivary cortisol will be used in this study.

Rimes *et al.* (unpublished-b) reported reduced cortisol output over the day (area under curve day; AUCday) in female adolescents with CFS. They also reported that lower AUCday in the CFS patients was significantly correlated with higher ratings of perfectionism in the child. This was the first study to make such comparisons. The comparison will be repeated here along with other clinical measures.

The social performance task used in this study is taken from a study used in social phobia (Rapee & Lim, 1992). Typically, when investigating cortisol response to stress, the Trier social stress task (TSST) (Kirschbaum *et al.*, 1993) is used. It was not used in the current study as it was considered inappropriate for the age group (see chapter 5). Cortisol responses to the stress inducing task (TSST) have been reported to increase significantly, peaking at about 10 minutes post task. These findings suggest that approximately 70% of participants tend to increase by about 2.5nmol/l in response to the task (Kirschbaum *et al.*, 2008).

Cortisol levels were measured in the current study to investigate the cortisol response profile in the 3 groups in response to a stress inducing task (the social performance task; chapter 5).

Hypotheses

Under the stress of being asked to give a brief presentation, cortisol levels of all adolescents will increase. Adolescents with CFS will show a flattened cortisol response and females with CFS in particular will show this pattern of disturbed cortisol responses compared to the other two groups. The adolescents with CFS will have lower cortisol output.

Methodology

Design

This study was a 3*6 design; there were 3 groups and repeated factors in terms of multiple collections of saliva samples (6 samples).

Procedure

This part of the study was conducted during the one-off task session. All participants were asked to complete 6 saliva samples at 6 specific time points described below. Participants were asked not to eat for 2 hours (but at the very least 30minutes) prior to the task session if possible and a recording was made if this was not adhered to. They were also asked to record what they had eaten so far that day. Medication use was recorded as well as stage of menarche for female participants, exercise undertaken during the last 24 hours, any current illness (aside from chronic condition in clinical groups) and time awoken.

Participants

Sixty-two adolescents with CFS, 78 healthy control adolescents and 31 adolescents with asthma completed the tasks. Due to refusals and incomplete samples, the final numbers in each group were 54 adolescents with CFS, 26 adolescents with asthma and 69 healthy controls. Table 7.1 outlines the reason for missing samples.

Table 7.1: Missing cortisol data

	CFS (N)	Asthma (N)	Healthy controls (N)
Refusals	2	2	7
Incomplete samples	6	3	4

Social Performance Task (described in full in chapter 5)

Participants were asked to give a 3 minute speech to the experimenter, which was videotaped. They were told that the experimenter would be evaluating their performance and that the video was being made to allow an evaluation of their performance by independent raters at a later point. The task elicits a level of stress that is manageable for the participants (Rapee & Lim, 1992). This task has been used before, and the same standardised procedure is used here as in the Rapee and Lim (1992) study investigating adolescents with social phobia.

Data collection

All adolescents were asked to complete 6 saliva samples before and after the social performance task. The time points were:

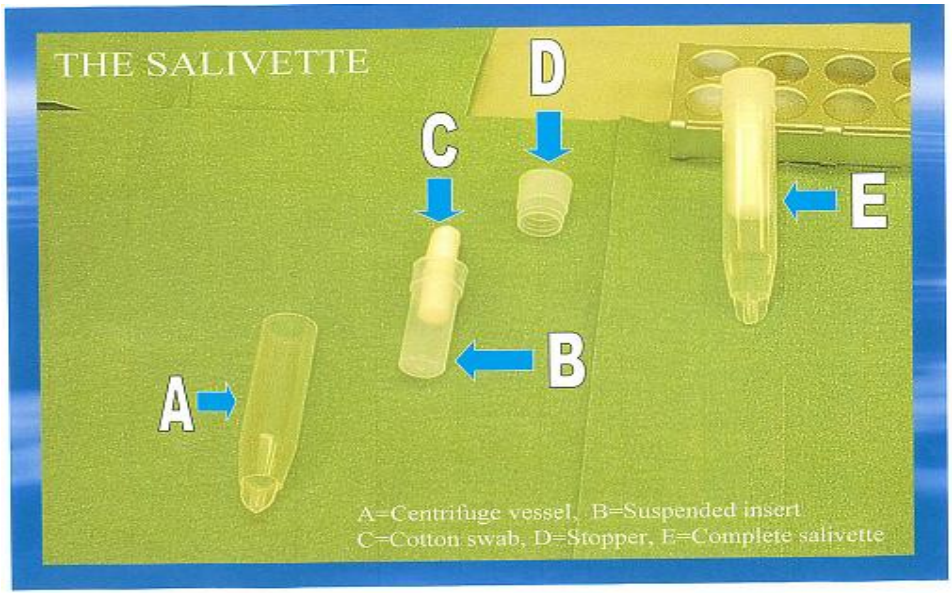
- 10 minutes after arrival at the task session (1)

- 10 minutes before social performance task (2) - this also constitutes a post-break baseline and will be used for AUC analyses
- 1 minute before social performance task (3)
- 10 minutes after task (4)
- 20 minutes after task (5)
- 30 minutes after task (6)

To collect the saliva, participants were asked to chew gently on a cotton swab for a period of 2 minutes and then to place the swab back in to the salivette. It is advised that the minimum volume of saliva recovered should be 1 ml of saliva and it was recommended that 2 minutes would be long enough duration to collect this volume confidently (Dr Andrew Papadopolous, Bethlem Royal Hospital). Figure 7.2 demonstrates the different sections of the salivette. Each salivette was individually labelled with the participant ID as well as the sample number (as indicated in brackets above). After the task session, all salivettes were stored in a freezer in the department at King's, before being transferred to the Bethlem Laboratory for analyses. Methods of collection and storage of the saliva samples were standardised in order to ensure that the measurements were reproducible and meaningful.

All participants were asked a series of questions regarding potential confounders of cortisol production. These were recorded by the researcher at the beginning of the task session on a separate document (see appendix 26, page 502), as outlined in the procedure section above.

Figure 7.2: An image to show the sections of the salivette



Analysing the samples

All participant samples were taken to a specialist laboratory at the Royal Bethlem Hospital for analyses having been stored in a freezer at King's College Hospital after task session sampling. Concentrations of cortisol in the saliva are much lower than those of general chemistry analytes and specialised laboratory techniques are necessary to measure these low concentrations. An immunoassay analyser was used in this study, more specifically a competitive immunoassay. The term competitive immunoassay refers to a measurement method in which an antigen (e.g. a hormone like cortisol) in a specimen competes with labelled reagent antigen for a limited number of binding sites on a reagent antibody.

Salivary cortisol concentrations were determined using the chemiluminescence assay of "Immulite". This chemiluminescence is used to label the antigen. The Immulite system used was developed by Diagnostic Products Corporation (DPC) and is a 'continuous, random-access automated immunoassay analyser designed around a proprietary assay tube called a test unit which allows for thorough and efficient washing of an integral

antibody or antigen-coated bead by rapidly spinning the tube on its vertical axis' (Babson, 2005). This equipment is in the laboratory at the Bethlem Royal Hospital and the team there conducted all of the analyses on raw data. More information is available in appendix 27 page 503.

Area under the curve

Research (e.g. (Roberts *et al.*, 2004)) conducted to investigate the consequences or responses to stress often use the area under the curve method of cortisol analysis when there are repeated measurements (time points). It is a useful physiological indicator of the sensitivity of the HPA axis. There are several parameters used to investigate the relationship between stress and health using area under the curve analyses.

There is a need to derive two forms of area under the curve to fully summarise the measurements. These are area under the curve with respect to ground (AUC_G) and area under the curve with respect to increase (AUC_I). An advantage of the AUC method is that it transforms the multivariate data (i.e. various time points are usually recorded as separate variables) into univariate space, especially when there is a need to summarise a lot of information. In addition it reduces the number of comparisons needed between groups.

Studies by Pruessner *et al.* (2003) and Fekedulegn *et al.* (2007) present formulae for the calculation of these two types of AUC that reveal different information embodied in the repeated measurements. AUC_G is the total area under the curve of all measurements. It takes into account both the intensity, which is described as the distance of the measurements from the ground as well as sensitivity, as characterised by the difference between the single measurements from each other (Pruessner *et al.*, 2003). Secondly,

the AUC_I is calculated with reference to the baseline measurement and it ignores the distance from zero for all measurements and emphasizes the changes over time.

The AUC_G is associated with being a measure of total hormone output. With the AUC_I it is a parameter concerned with the changes over time, related more to the sensitivity of the system.

In this study, there was agreement amongst researchers that the most appropriate point to start the AUC analysis was baseline2 (after the break). This officially marked the start of the specific task, discounting any other possible confounding task before it. This is the most reliable start point for AUC analyses.

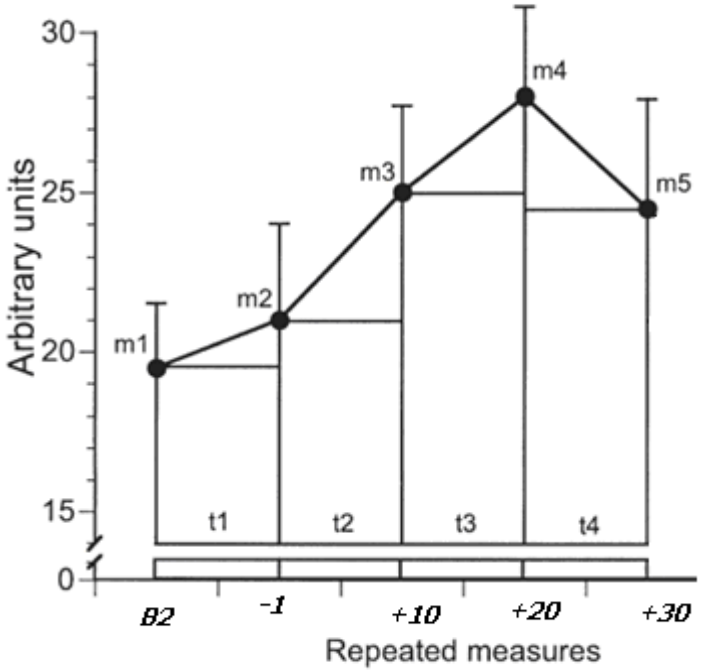
Data Analyses

The raw data generated by the methods described above were extracted and inputted to an excel document for each individual participant at the laboratory. Data were than merged to the SPSS data file for analyses.

All data (AUC_I and AUC_G) were explored for normality. Data was inspected visually using histograms, quantile-quantile plots and boxplots. No serious violations of normality were identified for these variables. However, some outliers were detected by inspecting the Q-Q plots, over and above those manually removed already. On statistical advice, outliers were considered to be scores that fell outside the range -2.5 to +2.5. Where outliers were identified, the analyses were repeated with and without these outliers. This led to no changes to the results. Subsequently; outliers were not removed from the final analyses. Parametric tests were therefore completed; various ANOVAs with factors of time, group and gender, as well as ANCOVAs where necessary.

AUC_G and AUC_I were employed to estimate circadian changes of cortisol to assess the overall secretion over the specific time period surrounding the social performance task (Pruessner *et al.*, 2003). A chart separated into rectangles is illustrated in figure 7.3, showing both the time segments and the specific points used in the formulae.

Figure 7.3: The relevant points/segments for AUC calculations (Fekedulegn *et al.*, 2007)



The information needed in order to calculate the formula consists of (a) the measurements themselves and (b) the time distance between the measurements. The measurements have been named m1 through m5, and the time distances named t1 through t4.

The formulae used in this study were adapted from Fekedulegn *et al.* (2007) and Pruessner *et al.* (2003);

Area under the curve ground (AUC_G) = [((Baseline2+one_minute)/2)*10]+[((one_minute+ten_minutes_post)/2)*15]+[((ten_minutes_post+twenty_minutes_post)/2)*10]+[(twenty_minutes_post+thirty_minutes_post)/2)*10]

Area under the curve increase = Area under the curve ground – Area under the curve baseline

Analyses were repeated excluding participants who may be depressed or anxious to check whether any group differences could be accounted for by these factors. After excluding participants who scored 13 or above on the Children's Depression Inventory - the cut-off score for likely depressive disorder on this scale - there were 40 CFS patients, 67 healthy controls and 26 asthma patients. The same procedure was carried out for the Social Phobia and Anxiety Inventory completed by participants. Here, the clinical cut-off score is 18 or above. The remaining CFS patients for this analysis were 51 CFS, 21 asthma and 64 healthy controls.

The analyses were also carried out excluding participants who reported taking medications that may potentially impact upon cortisol production. All in the CFS group, these were the contraceptive pill (4), melatonin (2), amitriptyline (3), fluoexetine (1), unspecified meds/anti-depressants (2), tetralysol antibiotic (1), Ritalin (1) and thyroxin (1).

It is important to note here that it is possible that asthma medications may influence their cortisol production. A range of studies have observed differing findings with regard to cortisol output (e.g. a review (Lipworth, 1999)). In this study all participants

were taking asthma medication. None of the participants had been on oral steroids at the time of testing for their asthma.

Further exploratory analyses included Pearson's correlations to investigate the relationship between certain clinical measures completed in the questionnaire study and cortisol (appendix 29, page 506). Correlations for change in cortisol and change in self-reported anxiety are also reported.

Results

Potential confounders of cortisol production were recorded based on self-reports and data collected during the task session. These variables are recorded in table 7.2.

Table 7.2: Potential confounders of cortisol production; means and group comparisons (one-way ANOVAs or Chi-squared test)

	CFS	**Asthma**	**Healthy Control**	**Results**
Age (mean, years)	14.96	15.00	14.58	$F(2,191) = 1.292$, $p = .277$
Sex (gender = females)	67.1	48.4	61.5	$X^2 (2,194) = 3.362$, $p = .186$
Menarche (% female yes)	85.2	84.62	97.1	$\chi^2 (2,94) = 4.290$, $p = .117$
Time of day of sampling (% pm)	69	68	59	$X^2 (2,146) = 4.901$, $p = .086$
Anxiety (STAI-state) – immediately prior to task	39.53 (9.48)	34.85 (8.24)	31.63 (8.52)	$F(2,111) = 8.607$, $p = .000$*
Anxiety (SPAI-c)	13.06 (9.86)	10.93 (9.91)	10.06 (7.42)	$F(2,176) = 2.208$, $p = .113$
Depression (CDI)	14.34 (7.72)	7.24 (5.38)	5.64 (5.18)	$F(2,187) = 39.108$, $p = .000$*

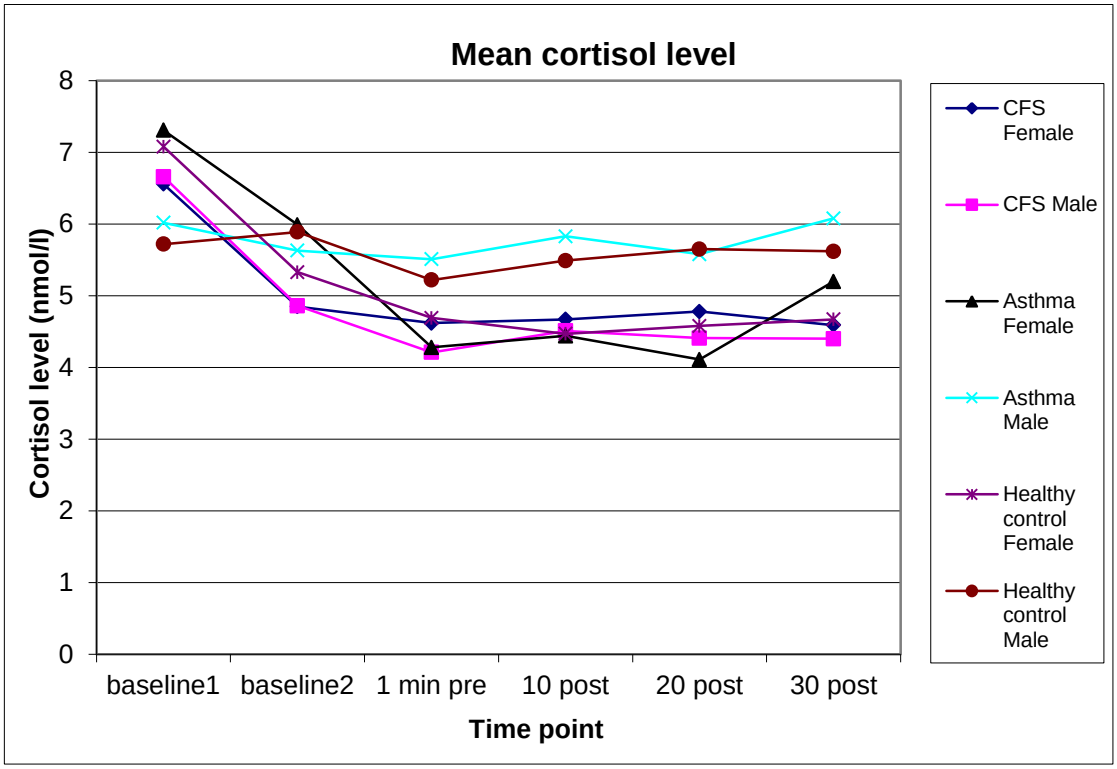
Repeated measures analysis

The repeated measures analysis revealed a within-subjects effect of time. Paired t-tests revealed that there was a significant difference between the two baseline scores and further significant differences from baseline2 to all other points, except 30 minutes post task with cortisol levels decreasing from baseline2. There was also a time*gender interaction. Post-hoc tests revealed there were no differences between genders at any of the 6 time points. For females, the same pattern as the whole group differences emerged (significant differences from baseline at 1 minute pre, 10 minute post and 20 minute post). For males, the significant differences were for baseline2 to one-minute pre with the cortisol levels across groups decreasing. There was not a significant interaction of time*group*gender, although it is approaching significance, so further investigation would be warranted.

Table 7.3: Repeated measures ANOVAs for all cortisol sampling points

	CFS	**Asthma**	**Healthy Controls**	**Result**
Baseline (at start of task session) (nmol/l)	6.59 (2.82)	6.88 (3.84)	6.52 (3.08)	Repeated measures ANOVA Within subjects: Time: F(5,640) = 23.459, p = .000* Time*group: F(10,640) = 1.268, p = .280 Time*gender: F(5,640) = 3.852, p = .018* Time*group*gender: F(10,640) = 2.167, p = .064 Between subjects: Group: F(2,128) = .846, p = .431 Gender: F(1,128) = .612, p = .435 Group*gender: F(2,128) = .307, p = .736
Baseline (after break) (nmol/l)	4.85 (2.40)	6.01 (3.22)	5.48 (2.43)	
1 minute before speech (nmol/l)	4.48 (1.96)	4.98 (2.79)	4.84 (2.14)	
10 minutes after speech (nmol/l)	4.62 (1.94)	5.24 (2.78)	4.82 (2.82)	
20 minutes after speech (nmol/l)	4.67 (1.90)	4.89 (2.93)	4.94 (3.30)	
30 minutes after speech (nmol/l)	4.54 (1.69	5.77 (3.15)	4.99 (3.18)	

Figure 7.4: Mean cortisol for all 3 groups at each time point



Initial analyses for area under the curve

There was a significant within subjects' difference on AUC_I, with a gender effect. Females had significantly lower scores on this variable than the males (p=.044*). No other significant differences emerged for AUC_I or AUC_G. Table 7.4 shows the findings for these analyses of whole groups (no exclusions).

Analysis of co-variance

Following these initial analyses, several clinical measures were controlled for in the analyses. However, none of these variables produced a significant finding. Table 7.5 shows the ANCOVA findings.

Correlations between cortisol and clinical measures

As part of the exploratory analyses, an association between the cortisol output and some of the clinical questionnaire measures was investigated (appendix 28 page 505).

Correlations investigated were AUC variables and the time of testing, social phobia/anxiety, self-oriented perfectionism, socially prescribed perfectionism and depression. However, no significant correlations were identified.

Correlations between change in cortisol and change in anxiety

Change between absolute baseline cortisol and cortisol 1 minute before task was calculated. There were no significant differences between groups on this change score. Change between baseline anxiety and anxiety immediately before the task was also calculated and again there were no significant differences between groups. The change scores were then correlated with each other. Here, there was a significant positive correlation in the CFS group (Pearson r = .375, p = .045*) but not in either of the other two groups.

Table 7.4: Area under the curve analyses for AUC_G and AUC_I; means, standard deviations and results of the repeated measures ANOVAs

	CFS (54; female 34)			**Asthma (26; female 14)**			**Healthy Controls**			**Result**
	All	**Female**	**Male**	**All**	**Female**	**Male**	**All**	**Female**	**Male**	
Area under the curve ground (nmol/l)	205.01 (77.41)	208.35 (76.32)	197.06 (82.52)	232.78 (125.77)	207.56 (90.80)	260.30 (155.35)	225.99 (118.35)	210.27 (97.80)	254.17 (146.41)	Between subjects effect: Group: F(2,128) = .993, p = .373 Gender: F(1,128) = 1.804, p = .182 Group*gender: F(2,128) = .928, p = .398
Area under the curve increase (nmol/l)	-1.68 (53.11)	-.830 (54.98)	-3.71 (50.42)	-28.02 (91.92)	-30.19 (108.84)	7.07 (54.43)	-23.59 (67.89)	-29.49 (52.68)	-13.02 (89.31)	Group: F(2,128) = 1.226, p = .297 Gender: F(1,128) = 4.132, p = .044* Group*gender: F(2,128) = 1.960, p = .145

Table 7.5: ANCOVA results for the cortisol data; controlling for different variables individually

	Time of day of sampling	**SPAI-C**	**Self-oriented perfectionism**	**Socially-prescribed perfectionism**	**Depression**
Area under the curve ground (nmol/l)	F(1,126) = .726, p = .396	F(1,123) = 2.891, p = .092	F(1,130) = 1.050, p = .307	F(1,130) = .086, p = .770	F(1,130) = .661, p = .418
Area under the curve increase (nmol/l)	F(1,126) = .887, p = .348	F(1,123) = 1.226, p = .270	F(1,130) = .708, p = .402	F(1,130) = .240, p = .653	F(1,130) = .350, p = .555

Excluding depression and anxiety

Participants that met the cut-off for the CDI and the SPAI-c (in separate analyses) were excluded. The results are in table 7.6. The depression cut-off for the CDI was a score of 13 or above and the SPAI-c cut-off was 18 or above. No significant differences emerged when excluding those adolescents who met clinical cut off for anxiety.

Table 7.6: Excluding anxiety and depression from the cortisol AUC analyses; one-way ANOVA results

	Excluding depression (scores of 12 or below)	**Excluding anxiety (scores of 17 or below)**
AUC Ground (nmol/l)	F(2,93) = 1.194, p = .715	F(2,92) = .932, p = .397
AUC Increase (nmol/l)	F(2,93) = .336, p = .715	F(2,92) = 1.528, p = .222

Excluding patients taking medication that may influence cortisol output

It was also considered important to exclude those taking anti-depressants and other medications that have been shown to influence cortisol levels (e.g. (Kirschbaum *et al.*, 1995) oral contraceptive; (Claustrat *et al.*, 2005) melatonin) The results are in table 7.7.

Table 7.7: Differences between the groups in those not on medication known to influence cortisol; one-way ANOVA results

	No medication participants only
AUC Ground (nmol/l)	F(2,120) = 1.183, p = .310
AUC Increase (nmol/l)	F(2,120) = 2.429, p = .092

When excluding these medications, there was a tendency towards significance on the $AUC_{I,}$ much closer to significance than when these participants had not been excluded.

Discussion

Main findings

When including all participants (not excluding for co-morbid diagnoses or medication), females across groups had significantly lower AUC_I than the males within the groups. This suggests that the females have lower change over time than the males, indicating a less sensitive HPA system (flattened cortisol response). There was a trend towards a significant interaction between group and gender. This was also reported in the Rimes *et al.* (unpublished-b) study. It is possible that this did not reach significance due to a power issue. There were no between group differences reaching significance.

Given the exploratory nature of this study and the lack of previous research, it was considered important to investigate possible associations between clinical measures and the cortisol output. However, this did not yield any significant correlations, which was contrary to the recent study by Rimes *et al.* (unpublished-b) that reported a significant correlation between high perfectionism and low area under the curve cortisol output over the day.

Further analyses involved excluding participants based on their scores for anxiety and depression. It was important to do this to check whether any possible group differences could be accounted for by these factors. After excluding depression and then anxiety in separate analyses, no further group differences emerged. Finally, when excluding medications known to influence cortisol levels neither of the two key parameters were

significant. AUC_I was tending towards significance again supporting the notion that CFS patients have a less responsive HPA system.

Previous literature

The idea that hypocortisolism may be a pre-existing risk factor for CFS is consistent with the idea that decreased levels of cortisol are available under conditions of stress. Although the only significant finding here is the lower AUC_I in females generally, the seemingly lower cortisol availability throughout is in line with this suggestion. The previously described case-control study (Segal *et al.*, 2005) reported adolescents with CFS had significantly lower mean cortisol levels than age matched controls in response to a low dose synacthen test (LDST). However, similar to this current study, Kavelaars *et al.* (2000) found no differences in baseline or corticotrophin releasing hormone (CRH) induced cortisol between 15 CFS patients and healthy controls. Wyller *et al.* (2010) found that serum cortisol concentrations in 67 adolescents with CFS were only slightly and non-significantly lower than levels in 55 healthy control adolescents. Clearly further investigation into the cortisol response profile in adolescents with CFS is warranted. It is possible that the evidence is not conclusive in the adolescent population because the adolescent HPA axis may still be developing / changing. Indeed it may be more flexible to situational changes than adults with CFS.

Salivary Cortisol

Many of the advantages of measuring hormones (e.g. cortisol) in saliva relate to the easy, non-invasive nature of the collection procedure. If the measurement of a hormone level in saliva is to be of general clinical value, it will need to be done on mixed (whole)

saliva. Certainly, for the collection of samples on this out-patient / control basis, mixed, whole saliva is the only practical alternative.

Mixed saliva usually contains suspended matter, including bacteria, leucocytes, oral squames and mucoid (Vining & McGinley, 1986). These may be denatured by freezing and thawing the sample. Workers have therefore advocated freezing and thawing and then centrifuging samples. This is all done before analyses (Vining & McGinley, 1986). Salivary cortisol samples minimise stress in comparison to the traditional method of venepuncture; both in terms of anticipation and pain (Vining & McGinley, 1987). Also, it facilitates multiple samples and avoids the need for cannula or several venepunctures. Finally, it facilitates the study of normal physiology. The easy, stress-free, non-invasive collection procedure greatly facilitates the study of normal subjects and children. This was previously impractical and such developments so can enlarge our knowledge of normal endocrine function. An excellent linear correlation has been shown between salivary cortisol and serum cortisol (Vining *et al.*, 1983). It is accepted as a valuable clinical and research tool.

Strengths / weaknesses of the study

There were no differences between the groups on age, gender, time of testing or menarche status in the groups. These are potential confounders of cortisol so this was very important to monitor during data collection and to match the groups as closely as possible. The CFS participants were consecutive patients at the CFS clinics, but it is possible that the sample may not be representative of the wider CFS population. Given that this study was cross-sectional in design, one cannot comment on whether the tendency towards lower levels of cortisol is an aetiological factor or a perpetuating

factor in the model of CFS. Indeed, changes in the HPA axis in patients with CFS might be an epiphenomenon of the illness rather than of particular etiological significance (Tomas *et al.*, 2013). It has also been argued that an adrenal insufficiency may simply be a secondary response to the illness (Papadopolous & Cleare, 2012).

In this study, there was generally a flattened response across groups in response to the social performance task. Possible reasons for this are that the task was not stressful enough for the participants. However, chapter 5 showed that anxiety did increase surrounding the task, particularly in the CFS group. It could also be because the 'stress task' was completed during a 2 hour task session. The session as a whole may have evoked a stress response thereby affecting the cortisol response. However, given the broad aim of the study it was impossible to complete the task on a separate occasion. Given the number of factors being investigated this potential methodological weakness could not be avoided. A true baseline cortisol measure was taken on arrival at the task session and all analyses were repeated using this baseline rather than task baseline but the findings remained the same.

Finally, this study used a standardised procedure. However, although participants followed exactly the same procedure and instructions, they were allowed to present on a topic of their choice. Perhaps presenting a topic of their own choice proved to be less stressful than the typical TSST where participants are told what they will be talking about (Kirschbaum *et al.*, 1993). Equating for prior knowledge was useful for this task, but perhaps not in terms of measuring cortisol output in response to stress. The TSST was not appropriate for this population as the child task was too young (asking participants to finish a short story) and the adult version too old (preparing for an interview). Results must be interpreted cautiously.

Clinical Relevance

Over recent years, there has been an increase in research into cortisol and its association with CFS (e.g. (Roberts *et al.*, 2008; Roberts *et al.*, 2004)). Irrespective of the initial cause, low cortisol may be one of the factors contributing to fatigue in CFS. Two recent studies support the potential clinical relevance of low cortisol in CFS (Rimes *et al.*, unpublished-a; Roberts *et al.*, 2008). Both found that patients with low cortisol levels do worse when treated with the usual recommended treatments for CFS than patients with normal or high levels of cortisol. Roberts *et al.* (2008) found that those who responded to CBT for CFS had higher pre-treatment urinary free cortisol levels. Non-responders were more likely to have hypocortisolism than responders. This study reported preliminary evidence that cortisol levels can normalise after CBT in adults with CFS.

The interaction of the HPA axis with other systems, such as immune dysfunction and neurochemical alterations, is beyond the scope of this chapter, although it is highly likely that such interactions are of importance in explaining the effect and implications for hypocortisolism in CFS.

Chapter Summary

There were no significant group differences on cortisol output, but there was a trend for the cortisol levels to be lower in CFS participants than the other two groups. There was a significant within group difference for gender. The female participants had lower cortisol levels than males, when all groups were analysed together. Support for the hypothesis that HPA axis changes develop as a consequence of CFS comes from the Roberts *et al.* (2008) study. This study found that treatment of patients with CFS with

CBT increased cortisol levels. However, it is clear, many gaps remain and thus any conclusions must still be treated with caution at this point.

Chapter 8: Prospective associations between beliefs, behaviours and maternal distress, and fatigue and functioning two months' later, in adolescents with Chronic Fatigue Syndrome

Synopsis

The objective of this prospective study was to test the hypothesis that cognitive and behavioural factors at time 1 would be associated with fatigue and related functioning 8 weeks later (time 2) in the CFS participants and the healthy controls.

Adolescents with CFS (N=85) and healthy adolescents (N=78) completed a second series of questionnaires at time 2. The main outcomes were fatigue (Chalder fatigue questionnaire), physical functioning (SF36; short form health survey, physical functioning subscale) and impaired functioning in daily activities (school and social adjustment scale).

A cognitive-behavioural approach led to the hypothesis that symptom focusing, negative beliefs about engaging in activity, avoidance of activity, perfectionism, unhelpful beliefs about emotions, all or nothing behaviours, anxiety and depression and maternal distress at time 1 would be associated with greater fatigue, physical functioning and school and social adjustment at time 2.

Multiple regression analyses in the CFS group revealed that all or nothing behaviour was associated with fatigue and physical functioning at time 2. Negative beliefs about engaging in activity were also associated with physical functioning at time 2. In the healthy controls, the multiple regression analyses indicated higher levels of maternal distress at time 1 was associated with worse school and social adjustment at time 2.

Fatigue and physical functioning at time 1 were associated with the fatigue and physical functioning scores at time 2 respectively.

This prospective study provides some evidence consistent with the hypothesis that cognitive and behavioural factors proposed as maintaining factors in a cognitive behavioural approach to CFS at time 1 were associated with fatigue and physical functioning eight weeks later. Negative beliefs about engaging in activity and all or nothing behaviour, may act to maintain fatigue and physical functioning in adolescents with CFS. There was no evidence that any other hypothesised factors (e.g. avoidance of activity) were significantly associated with fatigue, physical functioning or school and social adjustment at time 2 in the multiple regression models. The implications for cognitive-behavioural models and treatments are discussed.

Introduction

In the literature review (chapter 1), a multi-factorial model of CFS in adolescents was proposed. A distinction was made between predisposing, precipitating and perpetuating factors. The chapters in the thesis to this point have considered the cross-sectional data from stage 1; the questionnaire measures and the experimental tasks that were undertaken at baseline assessment. This chapter is focused on factors from time 1 that may be prospectively associated with fatigue, physical functioning and school and social adjustment (SASA) eight weeks later (time 2).

In adolescents with CFS there have been no prospective studies examining the role of hypothesised perpetuating factors derived from cognitive behavioural models such as negative beliefs about engaging in activity, avoidance of activities, symptom focusing and all or nothing behaviours. In this thesis, some of these factors were experimentally investigated and discussed (chapter 5).

Cognitive Behavioural theories of CFS

Cognitive behavioural theories informing therapeutic options for adolescents with CFS have been broadly based on models and research evidence in adults (e.g. (Surarwy *et al.*, 1995)). These models have been discussed in detail already in this thesis (chapter 1). In essence, Wessely *et al.* (1989) suggested that although fatigue may often have been initially triggered by an infection, other factors may then act to maintain the condition. Wessely et al. proposed that the individual starts to reduce their activity levels in an understandable attempt to feel less fatigued, but in fact this reduction in activity means that their exercise tolerance worsens. Fatigue increases when they try to do more. They

suggest that the individual ends up in a vicious cycle of unhelpful beliefs, activity reduction, exercise intolerance, fatigue and disability. This can contribute to the development of further distress, sometimes anxiety or depression of clinical severity, which in turn causes more fatigue and other physical symptoms in adolescents (Chalder *et al.*, 2002). Cognitive behavioural models in adolescents (Chalder *et al.*, 2002) suggest that similar factors in adolescents interact to prevent recovery. These models were based on clinical evidence in adolescents and the research base in adults. This study aims to investigate these associations further.

In the cross-sectional study (chapter 3), adolescents with CFS had significantly higher scores than the asthma group (other clinical illness group) for many of these model constructs; symptom focusing, catastrophizing beliefs, all or nothing behaviour, avoidance of activity, embarrassment avoidance, negative beliefs about engaging in activity and damage beliefs (all subscales of the Cognitive Behavioural Responses Questionnaire; CBRQ). It will be investigated whether these factors at time 1 are associated with fatigue and associated disability at time 2. An increased understanding of whether these factors act to perpetuate CFS will help develop better ways to treat CFS in adolescents. Possible maintaining factors will now be discussed in turn to explain the theoretical importance.

Negative beliefs about engaging in activity

Cognitive behavioural models of CFS in adults (Surarwy *et al.*, 1995) and adolescents (Chalder *et al.*, 2010) suggest that negative beliefs about engaging in activity e.g. "If I exercise too much, I may collapse" may act to maintain the fatigue and associated

symptoms. It is theorised that adolescents with CFS may develop such unhelpful beliefs because they have previously experienced a symptom increase after activity or exercise. It is proposed that those adolescents who have a fear that their symptoms will worsen after activities, will reduce their levels of activity and increase rest. It is possible that some adolescents with CFS may have had a pre-existing tendency towards being more anxious or neurotic (as reported in chapter 3). This general tendency could make them more vulnerable to developing fearful or catastrophic beliefs in the context of severe fatigue which worsens in the short-term after activity.

Petrie, Moss-Morris & Weinman (1995) reported from a cross-sectional study that adult patients with CFS who reported negative beliefs about activity had greater disability in terms of inactivity than the 'non-catastrophisers' as measured by questionnaire. Deale *et al.* (1998) reported that during cognitive behavioural therapy (CBT) for CFS in adults, changes in beliefs about activity and less avoidance behaviours were associated with improvement in functioning. These studies suggest that unhelpful beliefs about activity may act to maintain the fatigue until addressed in CBT. This has not been previously investigated in adolescents with CFS.

Avoidance of activity

According to cognitive behavioural models, prolonged rest and avoidance of activity is central in sustaining the cycle of symptoms and disability in CFS (Surarwy *et al.*, 1995). Sharpe *et al.* (1992) found that avoiding exercise predicted disability in adults with CFS (Sharpe *et al.*, 1992), while Ray *et al.* (1993) found an association between functional impairment and accommodating the illness in adult patients with CFS (Ray *et al.*,

1993). Further, Knudsen *et al.* (2011) reported that avoidance resting behaviours (avoidance of activity) were significantly higher in adults with CFS with long-term sickness absence in comparison to those with less work absence. Knudsen *et al.* (2011) used the CBRQ as in this thesis. Afari *et al.* (2000) conducted a study with adult monozygotic twins discordant for CFS, and reported that there were significantly higher levels of avoidance strategies (passive coping strategies) in the affected twins than in their non-affected co-twin. This supports the notion that avoidance of activity may act to maintain fatigue in CFS.

For the majority of patients and their families, rest appears an effective (or at least preferred) coping strategy because it reduces symptoms in the short term (Chalder *et al.*, 2002). However, the long term effects of decreased activity likely result in more symptoms at progressively lower levels of exertion. This will maintain, if not worsen the level of fatigue. Furthermore, avoidance of activity means that the accuracy of fearful or catastrophic beliefs cannot be evaluated by the patient and so will be continued. The impact of avoidance has not been previously investigated in a prospective study with adolescents.

All or nothing behaviours

Clinical experience has led researchers to suggest all or nothing behaviours are at the core of a model of CFS in adolescents (Chalder *et al.*, 2002). Patients will often develop a "boom and bust" approach to activity, characterised by periods of prolonged rest interspersed with bursts of activity. It might be rather than too much rest on its own, that fluctuations in activity are most problematic in maintaining fatigue (Moss-Morris *et al.*,

2011). Patients will overdo it when they feel good and then over-rest when they do not feel well enough to engage in activity. Activity becomes symptom dependent where the experience of symptoms dictates whether the patient can engage in activity. Moss-Morris et al.'s (2011) prospective study found that all or nothing behaviours were the most significant predictor of CFS 6 months after glandular fever. The same team's (Moss-Morris *et al.*, 2004) cross-sectional study found that all-or-nothing behaviours as measured by the CBRQ were strongly associated with fatigue in adults with CFS. All or nothing behaviours in the CFS group were significantly higher than the asthma group in the cross-sectional questionnaire study (chapter 3). This construct hasn't otherwise been investigated in adolescents to date.

Symptom focusing

It has been suggested that in an effort to control and reduce symptoms, patients become hyper-vigilant and over-sensitised to bodily symptoms (Chalder *et al.*, 2002). This symptom focusing may serve to exacerbate unpleasant sensations and has been shown to be associated with greater fatigue in adult patients with CFS in a cross-sectional study (Ray *et al.*, 1993). A greater focus on symptoms has been associated in another cross-sectional study with poorer quality of life in adolescents with CFS (Gray & Rutter, 2007).

As was alluded to in chapter 5, symptom focusing may act to maintain CFS by a) increasing the likelihood of noticing changes in bodily sensations and intensifying the symptom experience, both of which may then increase the likelihood of catastrophic misinterpretation and b) contributing to difficulties focusing on other internal and

external stimuli, i.e. concentration and distractibility problems (e.g. (Surarwy *et al.*, 1995)). A randomised control trial (Moss-Morris *et al.*, 2005) investigating the treatment effect of graded exercise therapy, the other recognised treatment option for CFS, reported that it was a decrease in symptom focusing rather than an increase in fitness that mediated the effect (improvement in condition). Another study (Wiborg *et al.*, 2011) reported that a decrease in focusing on the fatigue as measured by questionnaires, specifically contributed to the efficacy of CBT in adults with CFS and the level of fatigue and impairment decreased.

Perfectionism

Surawy and colleagues (Surarwy *et al.*, 1995) reported that adults with CFS in their clinic tended to have high standards for performance, personal conduct and were highly responsible. There is an assumption that the failure to meet these self-expectations would indicate a disappointment. This failure to meet perfectionist standards leads to increased effort which leads to exhaustion and increased levels of fatigue. A repeated experience of not achieving goals will reinforce negative beliefs that they are suffering an illness that they cannot overcome causing further distress and avoidance of activity (Surarwy *et al.*, 1995).

Moss-Morris *et al.* (2011) reported a prospective association between negative perfectionism and new-onset CFS suggesting that negative aspects of perfectionism may act to predispose an individual to developing CFS. The cross-sectional study in this thesis (chapter 3) reported higher levels of one aspect of perfectionism in adolescents with CFS than the control groups; the doubts about actions subscale (negative

perfectionism). This was the first study to investigate perfectionism in adolescents with CFS. Observations in the clinical setting in adolescents with CFS (Lloyd *et al.*, 2012) indicate a general tendency towards perfectionism, in many domains of life, which may contribute to the already discussed 'all or nothing' behaviour pattern.

Unhelpful beliefs about emotions

Surarwy *et al.* (1995) proposed within the cognitive behavioural model of CFS in adults that unhelpful beliefs about emotions may act to maintain CFS. These are beliefs about the unacceptability about experiencing or expressing emotions. This may be viewed as 'emotional high standards', relating to the perfectionism discussed above. It is possible that such unhelpful beliefs about emotions may perpetuate CFS by leading people to try to hide or ignore unwanted emotions. There is evidence that suppression of upsetting thoughts can lead to an inadvertent increase in distress (Wenzlaff & Wegner, 2000). Rimes and Chalder (2010) devised the Beliefs about Emotions Scale (BES). They reported that adults with CFS had more negative beliefs about experiencing and expressing emotions in the CFS group compared to the controls. However, in the current thesis (Chapter 3), the BES was used to compare the adolescents with CFS and the two control groups where no significant differences between groups emerged. This is the first study to investigate the BES as a predictor of subsequent fatigue and functioning in a prospective study in adolescents.

Depression and anxiety

A prospective study of young people found that anxiety and depression at time 1 were associated with increased fatigue and chronic fatigue 4-6 months later (Rimes *et al.*, 2007). It is suggested that this may be both a predisposing and perpetuating factor for CFS in young people. In adults, Moss-Morris *et al.* (2011) reported that anxiety and depression were associated with new onset CFS at 6 months post-infection (glandular fever). Pre-morbid psychopathology (anxiety, depression and psychosomatic illness) was associated with the development of CFS in a prospective study using the 1958 British birth cohort (Goodwin *et al.*, 2011). The literature in adolescents to date provides strong evidence of increased rates of psychiatric co-morbidity in adolescents with CFS compared to healthy or ill control groups (e.g. (Smith *et al.*, 1991)). However, this was all cross-sectional research, using a combination of questionnaire measures and semi-structured interviews. This is the first study to assess the prospective association between anxiety and depression and CFS in adolescents.

Maternal distress

Maternal distress may act to perpetuate CFS in the child. For example, anxious mothers may become more concerned about fatigue symptoms in their child and encourage avoidance of activity which inadvertently could maintain fatigue. In a large cross-sectional study in the community, mothers' psychological distress was associated with fatigue in the child (Chalder *et al.*, 2003). In the cross-sectional questionnaire study reported earlier (chapter 4), mothers of adolescents with CFS had significantly higher scores on subscales for anxiety and depression and general distress than mothers in the

control groups. In a further study, maternal distress at time 1 was significantly associated with new onset chronic fatigue and the persistence of fatigue in adolescents, 4-6 months later (Rimes *et al.*, 2007). This study was a prospective community study in 11-15 year olds. This needs further investigation in a CFS population and also in healthy controls given the findings of new onset fatigue. There is evidence of maternal distress being associated with a poor prognosis in childhood CFS (e.g. (Rangel *et al.*, 2000b)). It is possible that anxious mothers may be more focused on symptoms in their child. This could influence symptom reporting and help seeking behaviour.

Hypothesis for this study

In summary, cognitive-behavioural models of CFS have shaped the hypotheses for this study. It is hypothesised that negative beliefs about engaging in activity, avoidance of activity, all or nothing behaviours, symptom focusing, perfectionism, unhelpful beliefs about emotions, anxiety and depression and maternal distress at time 1 will be associated with greater fatigue, physical functioning and school and social adjustment (SASA) at time 2 (8 weeks later).

Methodology

Design

A prospective case-control study of adolescents with CFS as well as healthy controls was conducted. Participants completed self-report questionnaires at baseline and 8 weeks later.

Sample

Participants were all aged between 11 and 18. They were described in full in chapter 2. Of the 85 CFS patients that completed the questionnaires at time 1, 77 (91%) completed the questionnaires at time 2. In the healthy control group, 69 of the 78 participants (88%) completed the questionnaires at time 2.

Method

Eight weeks after the first stage of the study (baseline questionnaires), participants in the healthy control group and the CFS group were posted a further set of questionnaires. Those who failed to respond to the first contact letter were sent a reminder if the questionnaires were not returned in two weeks. They were offered the option of completing the questionnaires by email or over the phone with the researcher (author) if preferred. Only 2 participants completed the measures over the phone. They were both in the healthy control group. The participants in the CFS group did not receive treatment during this eight-week baseline period. They were on the waiting list for treatment to begin. A demographic questionnaire confirmed patients had not started any treatment, and confirmed no medication and contacts with GP related to their CFS. Five participants had seen the GP for recurrent infections between study visits.

Measures

The questionnaires used in this chapter have all been described in full in the cross-sectional questionnaire study chapters (chapters 3&4). No additional measures were used. The measures, and the subscales used were:

- Chalder fatigue questionnaire (CFQ) (Chalder *et al.*, 1993). This is a self-rated measure of the severity of fatigue that was chosen to assess the CFS symptom characteristics of this sample.

- Physical functioning subscale of the SF36. The SF-36 physical functioning sub-scale (Royal College of Physicians, 1996; (Ware *et al.*, 1992)) measures physical functioning.

- School and social adjustment scale (SASA) (Mundt *et al.*, 2002). The SASA is a self-report scale to investigate patients' perceptions of functional impairment.

- Cognitive behavioural responses questionnaire (CBRQ) (Moss-Morris & Chalder, 2003). This scale was devised to investigate patients' cognitive and behavioural responses to symptoms. The CBRQ was only recently devised and validated in a CFS population. This thesis is the first time it has been used in adolescents with CFS. The subscales are negative beliefs about engaging in activity (fear avoidance beliefs), catastrophizing beliefs, damage beliefs, embarrassment avoidance, all or nothing behaviour, avoidance of activity (avoidance resting behaviour) and symptom focusing.

- Child and adolescent perfectionism scale (CAPS) (Flett *et al.*, 1997). The CAPS was designed to measure self-oriented and socially prescribed perfectionism. Self-oriented perfectionism includes having strong motivations for oneself to be perfect, unrealistic standards for oneself, all or nothing thinking and maintaining a focus on one's own flaws. Socially-prescribed perfectionism is an interpersonal dimension involving perceptions of one's need and inability to meet the standards and expectations imposed by others.

- Frost multidimensional perfectionism scale (Frost *et al.*, 1990). The FMPS is a 35-item multidimensional scale to measure perfectionism. Setting excessively high

standards is the most prominent feature of perfectionism (Pacht, 1984). The scale has an overall perfectionism score as well as 6 subscales; concern over mistakes, personal standards, parental expectations, parental criticism, doubts about actions and organisation. This is a widely used scale in personality and clinical research (e.g. (Brown *et al.*, 1999)).

- Unhelpful beliefs about emotions scale (BES) (Rimes & Chalder, 2010). This questionnaire was designed to assess beliefs about the unacceptability of experiencing or expressing negative emotions.
- State-trait anxiety inventory (Spielberger, 1973). The STAI-C was developed to provide a reliable self-report scale for assessing state and trait anxiety for both research and clinical practice. The trait instructions asked them to indicate how they generally feel by reporting the frequency of occurrence of anxiety-related feelings and symptoms. The state instructions are to measure how the participant feels right now.
- Children's depression inventory (CDI). The CDI is a self-report inventory devised by Kovacs and Beck (Kovacs & Beck, 1977) to measure depression in children and adolescents. It is a widely researched and useful clinical tool.

Maternal questionnaires

- General health questionnaire (GHQ) (Goldberg, 1972). The GHQ-12 was used as a measure of current maternal mental health. The scale focuses on two major areas; the inability to carry out normal functions and the appearance of new and distressing experiences.

The only outcome measures being investigated were the fatigue (CFQ), school and social adjustment / impairment (SASA) and physical functioning (SF36). The other measures were all time point 1 variables. These time point 1 variables were completed

at time 2 (8 weeks later) to check for natural changes, whilst on the waiting list, before starting treatment. They were not being investigated as outcome variables.

Statistical Analyses

Characteristics of participants who took part in the study at both time 1 and time 2 were compared with those who took part at time 1 only using t-tests and chi-square analyses. Bonferoni corrections were used for the multiple comparisons. Mean scores for questionnaires completed at both time points (e.g. CFQ, SF-36 and SASA) were compared for the CFS group and healthy control group separately using t-tests and are in appendix 29, page 506.

Linear regression was used to investigate the association between the independent variables at time 1 (outlined in the method above) and dependent variables at time 2 (CFQ, SF36 and SASA).

A multivariate model was used to determine which factors were associated with fatigue (or physical functioning or school and social adjustment) at time 2. Variable selection was theory driven, where all variables included in the model were hypothesised to be acting to perpetuate the condition. Before completing any of the regression analyses, correlations between all variables were investigated. If two variables were found to be highly correlated with one another, the variable showing the strongest association in the preliminary univariate analyses was included in the multiple regression models. In multiple regression, these possible predictors are entered into the same model. A forced entry method was selected, which means all variables were forced into the model at the same time. This was used because it is an exploratory study, the first study of its kind in adolescent CFS. Variables that were shown to be associated significantly in the first regression analysis (model 1; $p < .10$ as recommended by a statistician) were entered

simultaneously again into a new model (model 2). This time the key factor (e.g. fatigue at time 1) was then also included in the fatigue model 2 after a first analysis with other factors only. These analyses were recommended and approved by the university statistician.

Results

Missing data

Table 8.1 shows the comparisons of time 1 scores between those that completed both time points and those adolescents that only completed time 1. This was done for the two groups separately. In the CFS group, the non-responders had significantly lower anxiety scores than the responders. The only significant difference in the healthy control group was the non-responders had significantly higher depression scores than the responders. However, the mean score in the non-responder group did not reach the clinical cut-off (13 or above) for depression.

Table 8.1: Independent t-tests and Chi-squared results to compare the questionnaire responders and non-responders on the time 1 questionnaire scores

		CFS	Healthy Controls
Age	Responders (mean & SD)	14.97 (1.76)	14.52 (1.42)
	Non-responders (mean & SD)	15.11 (1.54)	15.00 (1.30)
	Result	t(82) = -.22, p = .82	t(75) = -.91, p = .37
Ethnicity	Responders (N)	White 69, Other 6	White 61, other 5
	Non-responders (N)	White 9, Other 0	White 8, other 3
	Result	X^2 (1,84) = .78, p = .38	X^2 (1,77) = 3.93, p = .08
Gender	Responders (N)	Male 25, female 50	Male 28, female 41
	Non-responders (N)	Male 3, female 6	Male 2, female 6
	Result	X^2 (1,84) = .00, p = 1.00	X^2 (1,77) = .73, p = .47
Maternal GHQ	Responders (mean & SD)	13.28 (5.25)	11.20 (5.09)
	Non-responders (mean & SD)	12.44 (3.28)	14.00 (4.69)
	Result	t(81) = .47, p = .64	t(73) = -1.30, p = .20
Anxiety in the child (SPAI-c)	Responders (mean & SD)	13.93 (9.74)	10.42 (7.31)
	Non-responders (mean & SD)	3.22 (6.28)	8.18 (8.19)
	Result	**t(70) = 2.63, p = .01***	t(75) = .81, p = .42
Depression in the child (CDI)	Responders (mean & SD)	14.24 (7.46)	5.26 (4.96)
	Non-responders (mean & SD)	14.86 (11.14)	9.50 (5.88)
	Result	t(78) = -.20, p = .84	**t(75) = -2.25, p = .03***
Fatigue	Responders (mean & SD)	22.75 (6.35)	10.19 (3.82)
	Non-responders (mean & SD)	26.25 (3.58)	12.75 (2.76)
	Result	t(79) = 1.53, p = .13	t(75) = 1.84, p = .07

Comparison of questionnaire scores between times 1 and 2

Paired t-tests undertaken for each group separately indicated no significant change in questionnaire scores between times 1 and 2 for either group (see appendix 29, page 506

for results and means / SDs). This was true for all measures completed at both time points (see table 2.2 in methodology chapter). As mentioned above, this was a brief analysis to check for natural changes over time (8 weeks).

Univariate associations of fatigue and associated symptoms at time 2

Chronic Fatigue Syndrome

Table 8.2 presents univariate associations between variables at time 1 and fatigue, physical functioning and school and social adjustment at time 2 in the CFS group. In the CFS group, fatigue and depression at time 1 were associated with fatigue at time 2. Fatigue and physical functioning (SF36) at time 1 were associated with physical functioning at time 2. Fatigue, school and social adjustment, and depression at time 1 were associated with school and social adjustment at time 2.

Healthy controls

Table 8.3 presents the univariate findings for the healthy control group. In the healthy controls, fatigue, unhelpful beliefs about emotions and trait anxiety were associated with fatigue at time 2. Physical functioning and maternal distress were associated with physical functioning at time 2. Finally, maternal distress at time 1 was associated with school and social adjustment at time 2.

*Table 8.2: Univariate prospective associations between baseline psychological and behavioural variables and fatigue, physical functioning and functional impairment in **adolescents with CFS** (n=77) 8 weeks later*

Time 1 variables	Chalder Fatigue Questionnaire		Physical Functioning Subscale of the SF36		School and Social Adjustment Scale	
	β (95% confidence interval)	t value	β (95% confidence interval)	t value	β (95% confidence interval)	t value
Age (years)	.109 (-.54 – 1.51)	.94	.103 (-1.95 – 5.08)	.89	.090 (-.80 – 1.78)	.75
Chalder Fatigue Questionnaire (full 33 score)	.488 (.34 - .84)	4.71***	-.381 (-2.48 - -.67)	-3.48***	.387 (.25 - .94)	3.46***
Physical Functioning (SF36)	-.176 (-.12 - .38)	-1.52	.432 (.23 - .67)	4.06***	-.102 (-.13 - .05)	-.85
School and social adjustment SASA	.134 (-.10 - .38)	1.15	-.216 (-1.56 - .05)	-1.88	.350 (.16 - .74)	3.10**
Negative beliefs about activity CBRQ	.065 (-.36 - .65)	5.6	-.219 (-3.29 - .08)	-1.90	.009 (-.61 - .66)	.08
Catastrophising Subscale of the CBRQ	.147 (-.20 - .91)	1.27	-.147 (-3.09 - .69)	-1.26	.205 (-.09 – 1.29)	1.74
Embarrassment Avoidance CBRQ	.100 (-.21 - .52)	.86	-.073 (-1.62 - .85)	-.62	.190 (-.09 - .80)	1.61
All or Nothing Behaviour CBRQ	-.145 (-.64 - .15)	-1.24	.174 (-.33 – 2.35)	.14	-.118 (-.73 - .25)	-.99
Avoidance / Resting Behaviour CBRQ	.105 (-.19 - .50)	.90	-.045 (-1.42 - .96)	-.38	.031 (-.38 - .49)	.26
Symptom focusing subscale CBRQ	.018 (-.33 - .39)	.16	-.105 (-1.33 – 1.120)	-.17	.084 (-.29 - .60)	.70
Self-oriented perfectionism CAPS	.169 (-.12 - .76)	1.46	-.140 (-2.42 - .60)	-1.20	.199 (-.09 – 1.05)	1.69
Socially prescribed perfectionism CAPS	.034 (.29 - .78)	.27	.080 (-.64 – 1.29)	.67	.117 (-.18 - .52)	.97
Beliefs about Emotions Scale	.097 (-.08 - .19)	.82	.143 (-.17 - .72)	1.22	.075 (-.11 - .22)	.63
State Trait Anxiety Inventory – Trait	.155 (-.06 - .29)	1.29	-.071 (-.78 - .43)	-.59	.215 (-.02 - .40)	1.78

Children's Depression Inventory	.254 (.03 - .51)	2.21*	-.100 (-1.20 - .48)	-.85	.245 (.01 - .63)	2.08*
Maternal General Health Questionnaire	.052 (-.27 - .42)	.44	-.179 (-2.089 - .267)	-1.541	.082 (-.291 - .596)	.687

Significance level: * p < .05; ** p < .01; *** p < .001

There were no significant associations on the 6 subscales of the FMPS for any of the 3 outcome measures.

*Table 8.3: Univariate prospective associations between baseline psychological and behavioural factors with fatigue, physical functioning and school and social adjustment in the **healthy adolescents** (n = 67) 8 weeks later*

	Chalder Fatigue Questionnaire		**Physical Functioning Subscale of the SF36**		**School and Social Adjustment Scale**	
	β (95% confidence interval)	**t value**	**β (95% confidence interval)**	**t value**	**β (95% confidence interval)**	**t value**
Age (years)	-.010 (-.68 - .62)	-.09	.062 (-1.85 – 3.12)	.51	-.131 (-.37 - .11)	-1.08
Chalder Fatigue Questionnaire (33)	.592 (.39 - .79)	6.02***	.061 (-.70 – 1.16)	.50	.147 (-.04 - .14)	1.22
Physical Functioning (SF36)	-.146 (-.08 - .02)	-1.21	.289 (.05 - .43)	2.47**	-.010 (-.02 - .02)	-.08
School and social adjustment (WASA)	.149 (-.12 - .52)	1.23	-.101 (-1.74 - .71)	-.83	.031 (-.10 - .13)	.25
Self-oriented perfectionism CAPS	.083 (-.18 - .35)	.68	-.105 (-1.44 - .58)	-.85	.052 (-.08 - .12)	.42
Socially prescribed perfectionism CAPS	.115 (-.07 - .20)	.95	-.143 (-.830 - .21)	-1.19	.069 (-.04 - .07)	.57
Beliefs about Emotions Scale	.249 (.00 - .12)	2.09*	.040 (-.160 - .22)	.33	-.061 (-.03 - .02)	-.50
State Trait Anxiety Inventory – Trait	.242 (.00 - .17)	2.04*	-.233 (-.62 - .01)	-1.96	.016 (-.03 - .03)	.13
Children's Depression Inventory	.116 (-.10 - .27)	.95	-.201 (-1.29 - .11)	-1.68	.072 (-.05 - .09)	.60
Maternal General Health Questionnaire	.031 (-.16 - .21)	.26	.258 (.06 – 1.41)	2.18*	.250 (.00 - .13)	2.11

Significance level: * p < .05; ** p < .01; *** p < .001

There were no significant associations on the 6 subscales of the FMPS for any of the 3 outcome measures

Multivariate model of factors associated with fatigue and associated disability at time 2

Overview

In the introduction of this chapter, a cognitive behavioural model of CFS was outlined. In the multivariate analysis presented below, all variables that were hypothesised to be associated with fatigue (as well as physical functioning and SASA) in CFS were included in the multivariate regression models. This section will present the multivariate regression analyses for both the CFS and healthy control groups separately. The subscales of the FMPS were not included in the multivariate analyses as there would be too many variables for the models. Given that none of the univariate associations were significant for this scale, and the CAPS subscales were being included for perfectionism, it was deemed justified to use this approach.

The variables selected for the multivariate associations were theory driven, based on previous evidence in adults, as well as hypothesised models in adolescents with CFS. As this is an exploratory study, and the first of its kind in adolescent CFS, variables were included in the multivariate analyses regardless of univariate analysis outcomes. This allows for a thorough investigation into possible associations, even if part of a model rather than in a linear fashion.

Multivariate analyses – correlations between factors

Before conducting the regression analyses, correlations between all Time 1 variables were investigated (not including the 3 outcome measures). If two variables were found

to have a strong correlation with one another, the time 1 variable with the strongest univariate association with the time 2 factor was selected.

The variables that were significantly correlated with each other in the CFS group were trait anxiety and perfectionism (socially prescribed) (r = .497), unhelpful beliefs about emotions and perfectionism (socially prescribed) (r = .557), symptom focusing and catastrophising (r = .575), embarrassment avoidance and symptom focusing (r = .580), embarrassment avoidance and trait anxiety (.580), symptom focusing and trait anxiety (.529) and trait anxiety and depression (.690). As they were less strongly associated with the time 2 factors, trait anxiety, socially prescribed perfectionism, catastrophising and embarrassment avoidance were not included in the multiple regression models. All significant predictors in the first model (model 1), at the $p < .10$ level were entered into model 2 with fatigue (or physical functioning or SASA). Field (2005) recommends the use of $p < .10$ rather than the oft used $p < .05$ as it allows for the examination of residuals in the model. This was agreed by the statisticians at the university.

For the healthy adolescents, depression and trait anxiety were significantly correlated with one another (r = .728) as well as trait anxiety and unhelpful beliefs about emotions (r = .515). Trait anxiety was subsequently left out of the regression models.

Results for multivariate models

CFS participants

Fatigue

After the correlation analyses, 8 variables were left to include in the analysis (see table 8.4). A multiple regression analysis was carried out to investigate associations with fatigue at time 2. As reported in the statistical analysis section, fatigue was left out of the first run of the model. There was 1 variable significantly associated with the fatigue and this was included in a second model along with fatigue; all or nothing behaviour. Both fatigue and all or nothing behaviour at time 1 were significantly associated with fatigue at time 2 (see Table 8.4).

Table 8.4: Multivariate analyses of time 1 factors and the association with fatigue at time 2 in the CFS group

Model	Time 1 factor	Beta	Sig.	R	R^2	F-value
Model 1	Negative beliefs about activity	.079	.592	.351	.167	F(4,72) = 1.11, p = .370
	All or nothing behaviour	**-.238**	**.086**			
	Avoidance of activity	.088	.533			
	Symptom focusing	-.059	.693			
	Self-oriented perfectionism	.184	.155			
	Unhelpful beliefs about emotions	.036	.806			
	Depression	.220	.116			
	Maternal distress	-.002	.985			
Model 2	**All or nothing behaviour**	**.129**	**.004***	.505	.255	**F(2,70) = 11.97, p = .000***
	Fatigue	**.495**	**.000***			

Physical functioning

A multiple regression was carried out to investigate associations between factors at time 1 theorised to be associated with physical functioning at time 2 (table 8.5). Physical functioning assessed at time 1 was left out of the first model. There were 3 variables that were significantly associated with physical functioning and these were included in a second model along with physical functioning; perfectionism (self-oriented), negative beliefs about engaging in activity, all or nothing behaviour and physical functioning. Negative beliefs about engaging in activity and all or nothing behaviour at time 1 both added significantly to the model for physical functioning at time 2.

Table 8.5: Multivariate analyses of time 1 factors and the association with physical functioning at time 2 in the CFS group

Model	Time 1 factor	Beta	Sig.	R	R^2	F-value
Model 1	**Negative beliefs about activity**	**-.311**	**.032**	.428	.183	F(8,71) = 1.77, p = .100
	All or nothing behaviour	**.207**	**.098**			
	Avoidance of activity	.104	.449			
	Symptom focusing	.008	.956			
	Perfectionism (self-oriented)	**-.254**	**.043**			
	Unhelpful beliefs about emotions	.167	.243			
	Depression	-.090	.503			
	Maternal distress	-.048	.706			
Model 2	**Negative beliefs about activity**	**.381**	**.001**	.531	.282	**F(4,73) = 6.76, p = .000***
	All or nothing behaviour	**.301**	**.008**			
	Perfectionism (self-oriented)	-.177	.104			
	Depression	.118	.323			
	Physical functioning	-.182	.107			

School and social adjustment (SASA)

A multiple regression was carried out to investigate associations with SASA at time 2 (table 8.6). Baseline SASA was left out of the first model. Given the smaller number of participants completing this questionnaire (more missing data), the maternal distress variable was also left out of the model to allow for power issues. The univariate association was non-significant. There were 2 variables significantly associated with the SASA in this model and these were included in a second model along with school and social adjustment; perfectionism (self-oriented), depression, and SASA. Only SASA scores at time 1 were significantly associated with SASA scores at time 2.

Table 8.6: Multivariate analyses of time 1 factors and the association with school and social adjustment at time 2 in the CFS group

Model	Time 1 factor	Beta	Sig.	R	R^2	F-value
Model 1	Negative beliefs about activity	.012	.935	.357	.127	F(7,69) = 1.29, p = .270
	All or nothing behaviour	-.202	.143			
	Avoidance of activity	-.024	.866			
	Symptom focusing	.059	.685			
	Perfectionism (self-oriented)	**.222**	**.089**			
	Unhelpful beliefs about emotions	-.062	.671			
	Depression	**.249**	**.083**			
Model 2	Perfectionism (self)	.113	.332	.429	.184	F(3,69) = 4.58, P = .007*
	Depression	.118	.323			
	School and social adjustment	**.332**	**.007***			

Healthy controls

Fatigue

A multiple regression was carried out to investigate associations with fatigue at time 2 from the 4 variables theorised to be associated with fatigue in the healthy control group; perfectionism (self-oriented), unhelpful beliefs about emotions, depression, and maternal distress (table 8.7). Fatigue was left out of the first model. There was 1 variable significantly associated with the fatigue in this model; unhelpful beliefs about emotions and this was included in a second model along with fatigue. Fatigue at time 1 added statistically significantly to the model of fatigue at time 2, $p < .05$.

Table 8.7: Multivariate analyses of time 1 factors and the association with fatigue at time 2 in the healthy controls

Model	Time 1 factor	Beta	Sig.	R	R^2	F-value
Model 1	Depression	.039	.764	.259	.067	F(4,62) = 1.11, p = .358
	Perfectionism (self-oriented)	.035	.786			
	Unhelpful beliefs about emotions	**.225**	**.100**			
	Maternal distress	-.035	.778			
Model 2	Unhelpful beliefs about emotions	.175	.133	.423	.179	F(2,67) = 7.10, p = .002*
	Fatigue	**.350**	**.003**			

Physical functioning

A multiple regression was carried out to investigate associations with physical functioning at time 2 (table 8.8). Physical functioning was left out of the first model. Depression statistically significantly added to the model and was included in a second

model along with physical functioning. Physical functioning at time 1 added statistically significantly to the model of physical functioning at time 2, $p < .05$.

Table 8.8: Multivariate analyses of time 1 factors and the association with physical functioning at time 2 in the healthy controls

Model	Time 1 factor	Beta	Sig.	R	R^2	F-value
Model 1	**Depression**	**-.353**	**.006**	.381	.145	F(4,62) = 2.64, p = .042*
	Perfectionism (self-oriented)	-.113	.364			
	Unhelpful beliefs about emotions	.205	.120			
	Maternal distress	.171	.154			
Model 2	Depression	-.123	.320	.312	.097	F(2,68) = 3.56, p = .034*
	Physical functioning	**.251**	**.045**			

School and social adjustment

A multiple regression was carried out to investigate associations with the SASA scale at time 2 (table 8.9). School and social adjustment was left out of the first model. Maternal distress was statistically significantly associated with school and social adjustment at time 2 and was included in a second model along with school and social adjustment. Maternal distress at time 1 added statistically significantly to this model at time 2. However, the overall model did not statistically significantly predict school and social adjustment.

Table 8.9: Multivariate analyses of time 1 factors and the association with SASA at time 2 in the healthy controls

Model	Time 1 factor	Beta	Sig.	R	R^2	F-value
Model 1	Depression	.079	.544	.268	.072	F(4,62) = 1.20, p = .318
	Perfectionism (self-oriented)	.065	.619			
	Unhelpful beliefs about emotions	-.087	.523			
	Maternal distress	**.232**	**.065**			
Model 2	**Maternal distress**	**.275**	**.035**	.258	.067	F(2,66) = 2.35, p = .103
	School and social adjustment	-.069	.591			

Discussion

Overview of main findings

This prospective study was designed to test hypothesised maintaining factors for CFS in adolescents and was derived from a cognitive behavioural approach. It was hypothesised that negative beliefs about engaging in activity, avoidance of activity, all or nothing behaviours, symptom focusing, perfectionism, unhelpful beliefs about emotions, depression and anxiety and maternal distress at time 1 would be associated with greater fatigue, and poorer physical functioning and school and social adjustment at time 2 (8 weeks later). The main findings are outlined before discussing individual factors in turn.

Multiple regression analyses, in which the baseline scores of the three main outcome measures were also entered as potential predictors, indicated that for the CFS group, **all or nothing behaviour** and fatigue at time 1 were associated with fatigue at time 2. In

the univariate analyses, in the CFS group, **depression** at time 1 was also associated with fatigue at time 2. **All or nothing behaviours, negative beliefs about engaging in activity** and physical functioning were associated with physical functioning at time 2 in multiple regression analyses. In univariate analyses, no other factors were further associated with physical functioning at time 2. Baseline school and social adjustment (SASA) was associated with SASA at time 2. In univariate analyses, **depression** was also associated with SASA at time 2 in the CFS group.

In the healthy controls, multiple regression analyses indicated that baseline fatigue, SASA and physical functioning were each associated with the same factor at time 2. In univariate analyses, **unhelpful beliefs about emotions** and **trait anxiety** were also associated with fatigue at time 2. **Maternal distress** at time 1 was associated with the child's SASA and physical functioning at time 2.

In the CFS group, the non-responders at time 2 had significantly lower anxiety scores than the responders. The only significant difference in the healthy control group was the non-responders at time 2 had significantly higher depression scores than the responders from time 1. However, the mean score in the non-responder group did not reach the clinical cut-off (13 or above) for depression.

Chronic Fatigue Syndrome

Negative beliefs about engaging in activity

In this study, negative beliefs about engaging in activity at time 1 were associated with worse physical functioning at time 2 in the multivariate regression analyses. This is consistent with cognitive behavioural models which propose that beliefs such as

"avoiding unnecessary activities is the safest thing I can do to prevent my symptoms from worsening" will result in avoidance of activities (Wessely *et al.*, 1989). It is suggested that this avoidance has the effect of worsening physical functioning and activity tolerance, and means that the accuracy of the beliefs is not open to evaluation. These kind of unhelpful beliefs are addressed in cognitive behavioural interventions. For example, adolescents with CFS are supported to set weekly activity targets to gradually increase activity despite their fatigue and disability. Over time they often observe that although there may be short-term increases in fatigue after activity, in the longer-term their functioning improves. This is the first time negative beliefs about engaging in activity have been prospectively investigated in adolescents but adds support to the cross-sectional literature in this thesis (chapter 3) and in adults (Petrie *et al.*, 1995). Deale *et al.* (1998) further reported that during CBT for CFS in adults, changes in beliefs about activity and less avoidance behaviour were associated with improvement in functioning.

All or nothing behaviour

It is likely that these unhelpful beliefs about the consequences of activity may contribute to patients adopting an 'all or nothing' behavioural pattern. For example, when their fatigue worsens, beliefs that activity is harmful may be associated with the person undertaking a great deal of rest. Cognitive behavioural approaches propose that when symptoms improve, the individual tends to push themselves hard and that these behavioural extremes may maintain fatigue and poor functioning. Consistent with this hypothesis, in the present study, baseline all-or-nothing behaviours were significantly associated with both higher fatigue and worse physical functioning at time 2 in the

adolescents with CFS. This is consistent with a previous prospective study in adults (Moss-Morris *et al.*, 2011). Moss-Morris et al. reported all or nothing behaviours assessed at the time of glandular fever infection were the most significant predictor of CFS onset 6 months later. This fluctuation in activity levels is addressed in CBT. Patients are encouraged to first develop a consistent routine to avoid this 'boom and bust' approach to activity.

Perfectionism

In this study, self-oriented perfectionism was statistically significant in the first multivariate model of physical functioning and school and social adjustment in the CFS group. However, it did not remain significant when the baseline physical functioning and SASA were included in the respective models. This may indicate that perfectionism is not playing such a significant role in the maintenance of fatigue and associated impairment in adolescents with CFS as was expected. As has already been discussed in this thesis, perfectionism as a construct is not well understood in this population so further studies would be warranted to try and establish a clearer picture. It is possible that perfectionism didn't emerge here due to any previous perfectionist tendencies not currently being an issue given the adolescent's lack of involvement in education and activities. It has been suggested that the symptoms or diagnosis allow young people a way of avoiding blame for not maintaining high standards. There may also be measurement issues with the questionnaire used not being suitable for assessing individual aspects of perfectionism which other research and clinical anecdotal evidence suggests is present in adolescents with CFS (Chalder *et al.*, 2002; Fry & Martin, 1996). In the univariate analyses, the FMPS was also tested, but no significant associations

emerged. The FMPS and CAPS were well correlated. Due to sample size issues, the FMPS was not used in the multivariate models. There would be too many variables for the models. Given that none of the univariate associations were significant for this scale, and the CAPS subscales were being included, it was felt justified to use this approach.

Depression and Anxiety

Baseline depression was significantly associated with both fatigue and school and social adjustment at time 2 in the univariate analysis. In the multivariate models, depression was significantly associated with school and social adjustment in model 1, before baseline school and social adjustment was added. This is consistent with a previous community study of predictors of chronic fatigue in which depression and anxiety at time 1 were significant predictors of chronic fatigue 4-6 months later (Rimes *et al.*, 2007). These findings are supported by cross-sectional evidence that there are increased levels of psychiatric disorder in adolescents with CFS than healthy controls (Garralda & Rangel, 2005). Moss-Morris *et al.* (2011) reported that anxiety and depression were prospectively associated with new-onset CFS and pre-morbid psychopathology (anxiety, depression and psychosomatic illness) was associated with the development of CFS.

The prospective association between depressed mood and subsequent fatigue and SASA is possibly due to the overlapping criteria in the definitions of CFS and depression. However, it is also possible that psychological problems play a contributory role in the development of fatigue syndromes. Alternatively, psychological conditions and fatigue syndromes may share common risk factors that account for the association between

them. Depression may also contribute to the maintenance of fatigue other than at a symptomatic level as depression is associated with reduced motivation and behavioural avoidance (Smith, 2013). It will be important when health professionals consider the various factors that may be maintaining a young person's CFS, to assess for emotional difficulties, namely low mood.

Factors that were not associated with fatigue and associated symptoms at time 2

Symptom focusing

In this study, symptom focusing at time 1 was not significantly associated with fatigue and associated impairment at time 2 in the CFS group in the univariate analyses, or the multivariate analyses. This is contrary with a cross-sectional study in adults which found that symptom focusing was associated with greater fatigue (Ray *et al.*, 1993), the cross-sectional results in this thesis (chapter 3) and the graded exercise treatment trial which found that decreases in symptom focusing mediated outcome in adults with CFS (Moss-Morris *et al.*, 2005). It is possible that it didn't emerge as a significant predictor in the multivariate analyses, due to symptom focusing being quite highly correlated with other measures (e.g. negative beliefs about engaging in activity, Pearson's correlation = .414).

Avoidance of activity

Cognitive behavioural approaches suggest that individuals with CFS use certain unhelpful coping strategies such as excessive rest and avoiding challenging activities

(e.g. (Surarwy *et al.*, 1995)). These may help to control fatigue in the short-term but in the long-term will inadvertently add to symptom severity and adjustment in daily living activities (Chalder *et al.*, 2002). This avoidance behaviour is likely to link to the negative beliefs about engaging in activity that was a significant predictor in this study. However, 'avoidance of activity' did not emerge as a predictor in the current study. It is possible that some of the avoidance of activity is explained by the negative beliefs about engaging in activity which has meant it has not emerged as its own factor here. Indeed, these two variables were quite well correlated (Pearson's correlation = .419). Deale *et al.* (1998) found that a change during CBT treatment in negative beliefs about activity and less avoidance behaviour was associated with improvement in CFS patients. This suggests again that negative beliefs about activity may act to maintain the fatigue until addressed in CBT but also that the avoidance of activity may act in this way. However, Wiborg *et al.* (2011) did not find a significant relationship between fatigue and avoidance of activity in a study investigating CBT in adults with CFS. In the cross-sectional study (Chapter 3), avoidance of activity was significantly higher in the CFS group than the adolescents with asthma, so this factor merits further research attention. Other factors may lead to avoidance of activity and these may be the variables that emerge as significant instead of the avoidance of activity variable itself. It is a potentially complex relationship that demands further understanding.

Unhelpful beliefs about emotions

Contrary to the hypothesis derived from the cognitive behavioural approach, unhelpful beliefs about emotions did not emerge as a significant predictor of fatigue, physical functioning or school and social adjustment in adolescents with CFS. Possible reasons

why beliefs about emotions did not emerge as a significant finding in this thesis (either cross-sectionally or prospectively) when it is often reported clinically and has been shown in adults with CFS (Rimes & Chalder, 2010) is that there may be issues around an awareness of one's own emotions and one's beliefs about emotions at a young age. Some of the participants may be reluctant to acknowledge psychological risk factors, so such beliefs were not reported in the questionnaire. Unhelpful beliefs about emotions were significantly correlated with socially prescribed perfectionism (.519). Depression (Pearson's correlation = .316) was also quite well correlated with unhelpful beliefs about emotions. Beliefs about the unacceptability of expressing emotions have been linked with depression in adults (Jack, 1991).

Maternal distress

Another possible maintaining factor investigated in this study was the role of maternal distress, which had been found in a previous prospective study to be associated with the maintenance of chronic fatigue in adolescents (Rimes *et al.*, 2007). Surprisingly, this did not emerge as a significant factor, either in the multivariate models or the univariate analyses. In the cross-sectional study (chapter 4), maternal distress was significantly higher in the CFS group than either of the other two groups, so this issue requires continued research and clinical attention. In contrast, maternal distress was a significant predictor in the healthy controls and is discussed in a separate section below. It is possible that maternal distress did not emerge as a predictor in the CFS group because it is more of a risk factor than a perpetuating factor. It is also possible that other factors are having more of an impact on the perpetuation of fatigue and associated disability than distress in the mother.

Healthy adolescents

In the healthy controls different associations emerged to the group of adolescents with CFS. Baseline maternal distress was associated with school and social adjustment at time 2 in the multivariate analyses. Maternal distress was also associated with physical functioning in the univariate analyses. These findings suggest that perhaps maternal distress is important in the development or maintenance of fatigue before it becomes chronic to a clinical degree. For example, variation in maternal distress may play a more significant role in the early stages of fatigue than when it has become severe and chronic, when maternal concern may be the norm. These findings are consistent with the previous study by Rimes *et al.* (2007) in which maternal distress at time 1 was significantly associated with new onset chronic fatigue and the persistence of fatigue in adolescents, 4-6 months later. In the present study it was SASA rather than fatigue that was the outcome measure that showed the significant association. Similarly, in the adolescent anxiety literature, Spence *et al.* (2002) conducted a longitudinal questionnaire study and found that, maternal anxiety and depression were both associated with a significantly increased risk of developing symptoms of anxiety or depression in their child during adolescence.

It has previously been reported that those children who have parents with a psychiatric condition are more likely to have problems at school and socially, as well as increased somatic complaints (Downey & Coyne, 1990). This highlights the importance of assessing maternal health as well as the child's fatigue and disability at assessment as it may impact upon psychosocial status. It is possible that anxious mothers may be more focused on symptoms in their child. This could influence symptom reporting and help seeking behaviour.

Unhelpful beliefs about emotions and trait anxiety were associated in the univariate analyses with fatigue in the healthy control group. It is possible that unhelpful beliefs about emotions may contribute to fatigue by leading people to try to hide unwanted emotions which may be tiring in itself, or could lead to increased distress, resulting in increased levels of fatigue. Likewise, higher levels of anxiety may make people more vulnerable to fatigue due to heightened autonomic arousal or the effects of perseverative thinking. Each of these factors demands further investigation in the adolescent population.

Clinical implications

The findings from this prospective study provide some preliminary supporting evidence for some aspects of the cognitive behavioural model regarding the maintenance of CFS in adolescents. Crucially for treatment implications, this is the first time these cognitive and behavioural constructs have been investigated in adolescents with CFS in a prospective study. The findings about factors associated with fatigue and functioning in healthy adolescents may inform the development of early intervention strategies for CFS or chronic fatigue. For example, treatment could target activity scheduling and avoidance of activity generally. Cognitive behavioural interventions often focus on the perpetuating factors and are based on the constructs already described. Until now, the treatment of adolescent CFS has relied heavily upon the evidence in adults with CFS. This study adds support for some of the hypothesised maintaining factors in CFS and addresses how they may be important in the context of treatment. For example, these results support the CBT approach of addressing cognitive and behavioural responses such as negative beliefs about activity and avoidance behaviours. It is also important to

address the presence of anxiety and depression if relevant for the patient. As discussed earlier, these additional features may contribute to reduced motivation and treatment can address this too. These findings require replication and further investigation. Other maternal factors not assessed here may also be important, as may symptom focusing and other personality features that have not emerged or been investigated in this study. Future research should investigate these elements further with new prospective studies investigating cognitive behavioural features of CFS.

Methodological issues

There are some possible methodological issues to consider in this study. The cognitive behavioural responses questionnaire (CBRQ) used in this study has only been validated in adults, not adolescents. However, the reliability of the full scale and subscales were presented in chapter 3 and the Cronbach's alpha for the 7 subscales ranged from .752 to .906. This suggests it is a valid measure in this adolescent population. Possible drawbacks of this are that the questions or constructs were not well understood in the adolescent population but there were strong correlations between the maternal ratings of the child and the child rating themselves which suggests this is not the case. The other measures used had all been used on adolescents before and were reliable and valid.

Multiple regression analysis provides a powerful method to analyze multivariate data. Considerable caution, however, must be observed when interpreting the results of a multiple regression analysis. This study has included theory that has driven the selection of variables in the analysis. In this study, in the first instance, a simple linear regression was used where the outcome variable is predicted using one variable at a time. Multiple

regression is a natural extension of this method, where there are several predictors entered into the same model and how they are entered into the model is also important. Here, a forced entry method was selected, which means all variables are forced into the model at the same time. This was used because it was not known which factors were associated or may explain more of the variance in the model given this was the first study of its kind in adolescent CFS. To allow for a possible 'hierarchy' of importance, fatigue was not entered into the first model as it would likely explain a lot of the model. This is discussed further below. The models identified in this study require further investigation as to whether they can be generalized beyond the sample used to make inferences about these predictors. Although these factors are associated with fatigue and impairment at time 2, they only explain some of the variance in the model which suggests that other factors may be important. One must also mention the restrictions upon a study due to sample size. Due to the sample size (n = 80), it meant only a maximum of 8 variables could be included into a multivariate model. This is a common limitation faced in multivariate regression (Field, 2005) but must be acknowledged.

Several of the theorised variables / factors were correlated with each other. As a result only some will emerge as significant in multiple regression analyses. It is likely that fatigue being associated with fatigue and physical functioning associated with physical functioning is merely a marker of continuity as they persist over time. This is to be expected and so they were not included in the first round of models as it was assumed they would take up too much of the variance in the model. This is a feature of hierarchical regression and is a reliable option confirmed by the statistician at the university. Each of the factors significant in the first multivariate models was also addressed in this discussion in relation to how they may act to maintain CFS.

It is possible that the 8 week duration between time 1 and time 2 was not long enough to measure the factors associated with fatigue and disability at time 2 as very little had changed from time 1 to time 2. The 8 week duration was typically how long patients were waiting for treatment to start at the CFS units. It was deemed unethical to wait any longer before starting treatment. Future studies would benefit from following patients from the onset of fatigue which would make this prospective element longer. However, the cognitive and behavioural factors emerging do seem to mirror the adult findings which suggest that the 8 week duration was sufficient in starting to draw out the important predictive factors.

Chapter summary

This prospective study provides evidence that negative beliefs about engaging in activity, all or nothing behaviour and depression may act to maintain CFS in adolescents. In the healthy controls, baseline levels of maternal distress, unhelpful beliefs about emotions and trait anxiety were associated with fatigue and disability 8 weeks later. Further prospective studies investigating CFS in adolescents will add to our understanding of factors that act to maintain the condition. The next chapter brings these factors together into a hypothesised model of CFS in adolescents, in the overall discussion.

Chapter 9: Overall discussion

Synopsis

In this thesis a cross-sectional and prospective case-control design was used to test a hypothesised psycho-physiological model of CFS in adolescents. In this final chapter, the key results from all studies in the thesis are collated and discussed. These findings are used to generate a preliminary evidence based psycho-physiological model of CFS in adolescents. Clinical implications are considered as well as future directions for research proposed. Limitations of the studies in this thesis are discussed and overall conclusions drawn.

Introduction

This thesis investigated the hypothesised risk factors for CFS (e.g. psychiatric disorder, personality and self-esteem), and factors that may act to maintain the fatigue such as increased physiological dysregulation in response to stress, misattribution of symptoms, symptom focusing, sleep disturbance and fear leading to avoidance of activity.

Chapter 2 gave an overview of the methodology used in this thesis. It was a prospective case-control design with an 8-week follow-up. There were 3 groups; adolescents with CFS, adolescents with asthma and healthy control adolescents. The main contributory factors measured were physiological (heart rate, heart rate variability, skin conductance response and cortisol levels), psychological (e.g. negative beliefs about engaging in activity and all or nothing behaviours) and social factors (e.g. maternal distress or parental expectations). Experimental tasks were used to investigate responses to the anticipation and experience of attention, exercise and social stress tasks.

Main findings / components of the cognitive-behavioural (psycho-physiological) model of CFS in adolescents

A model incorporating all of the findings in this thesis, whilst drawing on existing adult and child models of CFS (e.g. (Chalder *et al.*, 2002; Surarwy *et al.*, 1995; Wessely *et al.*, 1989)) will be presented later in this chapter (Figure 9.1, page 359). First, each factor is individually discussed.

Predisposing or vulnerability factors

Psychological factors

Higher levels of anxiety and depression

There were significantly higher scores of anxiety and depression symptoms in the CFS group than the other two groups in the questionnaire study. Forty-four (51.8%) of the adolescents with CFS also met DSM-IV criteria for a psychiatric disorder (most frequently for anxiety and depression), as assessed by the Mini International Neuropsychiatric Inventory. It is possible that psychiatric conditions act as a risk factor for disabling fatigue and CFS and vice versa. It is also possible that genes, early life experiences and learned psychological responses act individually or together (e.g. via differences in HPA-axis responding) as risk factors for both psychiatric disorders and CFS. In the prospective study, in the CFS group, depression was significantly associated with both fatigue and school and social adjustment at time 2 in the univariate analysis. This is consistent with a previous community study of predictors of chronic fatigue (Rimes *et al.*, 2007). The prospective association between depressed mood and subsequent fatigue and social adjustment could be due to the overlapping criteria in the

definitions of CFS and depression. However, it is also possible that psychological problems play a contributory role in the development and maintenance of fatigue syndromes. Given that anxiety disorders and depression have been found to be associated with chronic fatigue and they occur at a similar stage of development it seems likely that these disorders have some common risk factors that account for the association between them. Depression may also lead to the maintenance of functional impairments associated with fatigue problems, particularly as depression is associated with reduced motivation and behavioural avoidance (Smith, 2013).

Higher social desirability

The adolescents with CFS reported significantly higher levels of social desirability than the other two groups. This trait has advantages in some contexts. However, it is theorised that in an attempt to behave in a socially desirable way, the adolescents are reluctant to reveal problematic emotions to others. Attempts at emotional suppression may interfere with effective emotional processing and the stress associated with concealing these emotions may also make an adolescent more vulnerable to symptoms of fatigue.

Higher neuroticism / lower extraversion

In this study, the CFS group had significantly higher scores of neuroticism and lower extraversion scores as measured by the EPQ. This supports the previous literature which suggested that certain personality traits, including rigidity, fearful behaviour and sensitivity were reported more frequently in adolescents with CFS (e.g. (Rangel *et al.*, 2005)). Neuroticism may predispose individuals to both depression and fatigue. Neuroticism is already demonstrated to be a factor that predisposes people to develop

depression (Duggan *et al.*, 1995). However, the neuroticism scale items overlap with depression (e.g. 'does your mood often go up and down'). Given this, it is perhaps unsurprising that when controlling for depression in the questionnaire study, the neuroticism subscale of the EPQ was no longer significantly different between groups. Neuroticism could be deemed to be a measure of emotional affect or instability. A reduced ability to adapt to stress may contribute to the development of CFS especially at times of increased demands such as changing school, exams or an acute illness, or in chronically stressful situations such as having a parent with mental or physical health difficulties.

Doubts about actions

This was the first study to investigate the role of perfectionism in adolescent CFS. The doubt about actions subscale of the FMPS in this study was significantly higher in the CFS group than either of the other two groups. The Doubt about Actions subscale of the Frost Multidimensional Perfectionism Scale is one of the subscales of negative / clinical perfectionism which is broadly understood to be maladaptive (White & Schweitzer, 2000). Cognitive behavioural models of CFS propose that perfectionism leads to increased fatigue and disability through a rigorous attempt to meet high standards (Surarwy *et al.*, 1995). A failure to meet these perfectionist standards leads to increased effort, which subsequently leads to exhaustion and increased levels of fatigue. The doubts about actions displayed by adolescents with CFS may make the adolescent vulnerable to stressful situations, due to increased doubts about their ability to complete tasks satisfactorily. This may work in a similar way to higher levels of neuroticism. Also, if an individual has significant doubts about what they can achieve, the result may be an avoidance of future attempts of the activity or exercise. It may also lead towards

all or nothing behaviours where patients give everything they can to an activity in order to achieve it, but then they must rest to recover.

Social skills / attention switching / communication problems in the child

Mothers in all 3 groups were asked to complete an Autism Spectrum Questionnaire (Baron-Cohen *et al.*, 2001). No link was being suggested between CFS and autism. The questionnaire subscales do however largely relate to difficulties reported to be problematic in adolescent CFS. The adolescents with CFS scored significantly higher on three of the subscales compared to the other two groups; social skills, attention switching and communication skills. These traits may predate the CFS, making the child more vulnerable to the condition, due to finding common situations more stressful, owing to increased social anxiety. Adolescents with CFS often report problems with aspects of attention (Haig-Ferguson *et al.*, 2009) and this is now reflected in a maternal report (attention switching). In the Haig-Ferguson et al. study, children with CFS, their parents and teachers alike described such problems. However, it is also possible that these difficulties are the result of fatigue or that the fatigue makes these difficulties more pronounced.

Time 1 factors associated with time 2 factors in healthy controls

Maternal distress was associated with physical functioning and school and social adjustment ratings at time 2 for the healthy control group. These findings suggest that maternal distress is important in the development or maintenance of fatigue / problems with functioning before it becomes chronic to a clinical degree. Maternal distress may play a significant role in the early stages of fatigue development. Clearly when fatigue

is chronic, maternal concern would be the norm. These findings are consistent with a previous study by Rimes *et al.* (2007) in which maternal distress at time 1 was significantly associated with new onset chronic fatigue and persistence of fatigue in adolescents, 4-6 months later. In the adolescent anxiety literature, Spence *et al.* (2002) conducted a longitudinal questionnaire study and found that, maternal anxiety and depression were both associated with a significantly increased risk of developing symptoms of anxiety or depression in their child during adolescence. The finding in this thesis must be interpreted with caution. The School and Social Adjustment Scale refers to 'illness' in the 5 items of the questionnaire. It assumes that there is an illness already present in the young person. This suggests that once there is an illness (of any kind) maternal health could be important.

Physiological factors (heart rate, heart rate variability, skin conductance response and cortisol)

Differences in physiological dysregulation responses in adolescents with CFS may provide evidence for a stress vulnerability factor in the development of fatigue. Results of psychophysiological differences were found in this study for both heart rate and skin conductance measures. Baseline heart rate variability (HRV; RMSSD) was significantly lower in the CFS group than either of the other two groups. Previous research has found that lower HRV is observed in adolescents with CFS (Wyller *et al.*, 2007b), fibromyalgia (Cohen *et al.*, 2000) and in depression and anxiety (Kemp *et al.*, 2012) compared to healthy controls. However, in this study, it could also be due to the stressful situation of hospital attendance. The CFS group also had significantly higher scores of all aspects of baseline skin conductance response (SCR) than the healthy adolescent / asthma participants. This is the first time that SCR has been investigated in

adolescents (or adults) with CFS. High baseline SCR indicates higher levels of arousal which may be associated with anxiety and stress. There were no significant correlations between the subjective ratings of anxiety and physiological dysregulation in terms of either heart rate or skin conductance at different time points, but dissociations between physiological measures of arousal and self-reports are not unusual (e.g. (Lang *et al.*, 1983; Newton & Contrada, 1992)).

The CFS group had a significantly higher SCR (integral; area under the curve) in anticipation of the speech task. On the min-max SCR measure the CFS group showed a significant increase from speech to recovery while the other two groups exhibited a non-significant decrease. This portrays a higher and more slowly declining SCR in the CFS group which suggests they recover more slowly from a stressful situation. Slower recovery from stress has been suggested before in somatic conditions (Krantz & McCeney, 2002). Similarly, the CFS group had significantly higher HR in anticipation of both the social performance task and the exercise task. There were no significant correlations between the subjective ratings of physiological dysregulation and heart rate. The CFS group had significantly higher HR during the recovery stage in line with the SCR data highlighting a slower recovery in the CFS group. It is possible this slowness in recovery in the CFS group is associated with psychological correlates. The CFS group may be ruminating about their performance afterwards more than the other two groups which could contribute to this prolonged 'stress state'. This could be investigated in future studies. Higher HR findings are in line with the previous literature in adolescent CFS (e.g. (Galland *et al.*, 2008)).

The LF/HF ratio (HRV) was significantly higher in the CFS group than the other two groups across the whole recording in accordance with the higher baseline LF/HF ratio discussed above. This dominance of the sympathetic relative to the parasympathetic

nervous system may indicate 'burn out' due to stress which has been considered possible in patients with CFS. It is suggested that a striving and perfectionist approach to life may be a premorbid characteristic of people with CFS, and eventually leads to individuals being consistently inactive or possibly "burnt out". Similarly, it has been suggested that sustained arousal may cause fatigue (Wyller *et al.*, 2009). It is possible that the current findings indicate a prolonged stress response in the CFS group. It is too early to draw conclusions on this finding, as the current study investigates adolescents who have already developed CFS. It cannot be ruled out that the psychophysiological changes are a result of the condition rather than a contributory factor.

There were no significant group differences on salivary cortisol levels, but there was a tendency for the cortisol levels to be lower in the CFS group than the other two groups. Previous studies investigating adolescent CFS reported similar findings (Wyller *et al*., 2010) using serum cortisol concentrations. Further salivary cortisol studies are needed, including within the home environment rather than a potentially stressful research testing situation. There was a significant within group difference for gender. The female participants had lower cortisol levels than males, when all groups were analysed together.

Social factors

Clinical characteristics of the mother

Higher levels of maternal distress and worse quality of life

There were significantly higher scores in the mothers of the CFS group on the GHQ and the HADS (anxiety and depression subscale) as well as the WHO-5. This suggests that the health, well-being and quality of life of the mothers' of adolescents with CFS are

generally worse than those mothers in the other two groups. These findings which highlight a significant level of maternal distress in this population are in line with the five cross-sectional studies (Chalder *et al.*, 2003; Missen *et al.*, 2012; Rangel *et al.*, 2005; Rangel *et al.*, 2000b; van de Putte *et al.*, 2006), all of which reported more maternal psychiatric symptoms and chronic health problems in the mothers of CFS patients when compared to healthy controls, juvenile arthritis and a better CFS outcome group. It is not clear whether the elevated maternal distress is due to the illness of the child and the understandable worry this causes, whether it pre-exists or whether both interact in a mutually unhelpful manner. It is possible that anxious mothers may be more focused on symptoms in their child. This could influence symptom reporting and help seeking behaviour. Cresswell, Schniering & Rapee (2005) reported significant correlations between child and parent anxiety. When children received treatment for anxiety, both they and their mothers subsequently reported a reduction in the interpretation of possible threats or stressors.

Over-protection; higher self-sacrificing behaviours, higher concerns about impact of illness and higher pre-occupation with their child's illness

The mothers of adolescents with CFS reported greater levels of self-sacrificing behaviours than the mothers in the other two groups. Although this study used a different measure, the findings are in line with the previous literature (Garralda & Rangel, 2005). Together they suggest greater emotional over-involvement from these mothers (Garralda & Rangel, 2005; Rangel *et al.*, 2005). Self-sacrificing behaviour is not necessarily the same as over-protection. A significantly lower percentage of mothers in the CFS group were in employment and this may be an example of self-sacrificing behaviour or over-protection. They may have taken the view that it was important to

stay at home to look after the ill child. However this is unclear as the reason for not working was not ascertained. Return to work for the mother could be an important stage in the child's recovery. Anecdotally, this has been reported as a difficult transition for the mother and child (personal communication) (Chalder, 2012). If the mother has given up work due to the child's illness, it could have a negative impact on her own quality of life and self-esteem and perhaps even their attitude towards their child. Ultimately it could lead the child to feel guilty, or it may contribute to the child feeling out of control. This is a complex issue that requires further investigation.

It could be argued that over-protection is a natural response to a chronically ill child, or may be in response to characteristics already shown in the child. However, it is also possible that parental responses may be acting inadvertently to perpetuate the fatigue and / or disability in adolescents with CFS. For example, in their understandable efforts to aid recovery, parents may be doing too much for their child in contrast to encouraging the young person to build up their activity levels which would facilitate confidence in coping with different situations. The illness burden of CFS on the child and their family is very different and indeed can be difficult to manage.

The Family Response Questionnaire revealed significant differences between the illness groups on responses of family members to people with a chronic illness. The scale was specifically designed with CFS in mind. The mothers of the CFS group scored significantly higher on the concerns-about-self subscale, showing greater concern about the effect the illness may have on her life. Further, the rejecting-hostile subscale was significantly higher in the mothers of the CFS group, which quantifies an attempt to minimise the complaints / symptoms of the ill family member. Finally, the sympathetic-empathic responses in the CFS group were higher than the mothers in the asthma group. This could reflect the perceived severity of the condition, with the mothers of the

adolescents with asthma having fewer concerns about the child's illness. It does highlight a certain pre-occupation with the illness in the CFS group, which is not necessarily beneficial to the child's recovery. It is possible that the high levels of distress in the mothers of the CFS adolescents results in them being unable to respond in the most helpful ways. Taken together, the findings of higher scores of rejecting behaviours in addition to higher scores of empathic behaviours do not satisfactorily fit into a model of CFS in adolescents. It is possible this pattern reflects a real battle for mothers of adolescents with CFS to know how best to deal with this debilitating condition. Sometimes empathy and concern may be considered helpful, other times rejection of the symptoms may be best for the patient. These responses are possibly a reaction to a condition that is poorly understood.

In the anxiety and depression literature, studies have reported that where there is low maternal care, or high maternal overprotection, there are higher levels of anxiety or depression in the child (Parker, 1979). A review of such childrearing practices (Rapee, 1997) reported a consistent pattern of rejection and control by parents being related to anxiety and depression in the child. Some of the literature points specifically towards rejection being associated with depression and over-protection associated with anxiety. Seemingly the two extremes are problematic. Indeed, Parker (1983) suggested that parental overprotection could be a risk factor for poorer psychosocial development. It is possible that CBT targeting parenting techniques or challenging general parent (dis)stress may be effective in reducing child distress. Family CBT may provide additional benefits to child-focused CBT alone (Wood *et al.*, 2006).

Maternal emotion regulation

The mothers of adolescents with CFS were found to have significantly higher questionnaire scores for concealing emotions. This strategy of not letting others see what they are feeling may be counter-productive for the mothers, and a maladaptive emotion control effort (Hayes *et al.*, 1999). This may be important for the child, as they may learn these approaches of emotion regulation from their family. In addition, the mother may not notice distress in the child and / or may interpret physical symptoms as signs of physical illness. Concealing their own emotions (mothers) may lead to these consequences through the inevitable stress caused by hiding one's emotions from those around them.

Higher maternal neuroticism

Mothers of adolescents with CFS had significantly higher levels of neuroticism than the mothers in the other two groups as measured by the EPQ. The link between neuroticism and distress is well established (for example neuroticism is associated with increased subsequent risk for a range of psychological disorders) and the mechanisms underlying this link have received considerable attention (e.g.(Bolger, 1990; Bolger & Schilling, 1991; McCrae & Costa, 1986)). Some authors argue that the measures are distinct, with neuroticism representing a stable personality trait, whereas psychological distress represents a present state (Rodgers, 1990). However, others argue that neuroticism as a tendency to experience distress may show continuity over time (Bolger, 1990). Neuroticism in the mother is undoubtedly important and may affect the child in a number of different ways. For example, it is suggested that higher levels of neuroticism in the mothers may result in the mothers having difficulty separating from the child due to their own anxieties. The mothers' worries may act to make the child more aware of

their symptoms and symptom reporting and concern about their symptoms may increase. This could contribute to the development of fatigue and poorer functioning. Interestingly, the mother's and child's neuroticism scores were not significantly correlated with one another.

Worse mood and atmosphere at home

On this measure of family functioning, there was only one significant subscale. All other subscales suggested that the CFS families were largely functioning in the same way as the control group families. The mothers in the CFS group reported significantly worse mood and atmosphere at home than the other two groups. This adds to the notion that distress in the family is a crucial factor in this condition, but given the cross-sectional nature, one cannot be sure about how the constructs are related. It is theorised that a worse environment at home may make the adolescent more vulnerable to stress or illness. It may impact upon the adolescent's mood, where low mood has already been presented as a potential risk factor in CFS. This was the first study in adolescents with CFS to investigate atmosphere at home specifically. In adolescents (aged 16), Tulisalo and Aro (2000) reported that worse atmosphere at home was associated with subsequent depression. There is nothing to suggest the same may not be true for adolescent CFS given the overlap in symptomatology.

Perpetuating / maintaining factors

Once fatigue has developed, it is proposed that additional factors act to perpetuate the fatigue which may be different to those that initially triggered it. Possible maintaining factors are discussed in turn below.

Beliefs about behaviour and behavioural responses

Prolonged rest, all-or-nothing behaviour and avoidance of activity are central in sustaining the cycle of symptoms and disability in cognitive behavioural models of CFS (Surarwy *et al.*, 1995; Wessely *et al.*, 1989). All or nothing behaviour as measured by the CBRQ was significantly associated with both fatigue and physical functioning at time 2 in the adolescents with CFS. Patients with CFS will often develop a "boom and bust" approach to activity characterised by periods of prolonged rest interspersed with bursts of activity. In essence, activity has become symptom dependent and as time goes on, the symptoms become more and more controlling. These factors are all addressed in CBT with patients encouraged to first develop a consistent routine to avoid this 'boom and bust' approach to activity. However this is the first study to provide evidence of their importance in adolescents with CFS compared to adolescents with asthma or healthy young people.

Consistent with this approach (Surarwy *et al.*, 1995; Wessely *et al.*, 1989), in the prospective study, negative beliefs about engaging in activity at time 1 were associated with physical functioning at time 2. It is suggested that young people with CFS may hold beliefs which result in reduced activity and worse physical functioning.

Avoidance of activity was significantly higher in the cross-sectional study in the CFS group than in the adolescents with asthma but was not a significant predictor in the prospective study. Avoidance is used in an attempt to control the symptoms, including

missing school or social activities. This inadvertently puts them at risk of becoming more isolated from their peers and increasingly behind with their school work which in turn leads to the maintenance of fatigue and other physical symptoms. Although avoidance may control fatigue in the short-term in the long-term it will add to symptom severity and disability (Chalder *et al.*, 2002).

Symptom focusing

It is suggested that in an effort to control and reduce symptoms, patients become hyper-vigilant and over-sensitised to bodily symptoms (Surarwy *et al.*, 1995). This may exacerbate unpleasant sensations and has been associated with fatigue in adults with CFS (Ray *et al.*, 1993). Consistent with this hypothesis, in the cross-sectional study, the CFS group reported significantly higher levels of symptom focusing than the asthma group. Yet, in the prospective study, symptom focusing at time 1 was not significantly associated with fatigue and associated impairment at time 2 in the CFS group, in the univariate or multivariate regression analyses.

To investigate symptom focusing further, a symptom focusing vs. distraction task was employed. The hypothesis that focusing on the causes, meanings and consequences of one's current symptoms, compared to distraction items, would result in significantly larger increases in fatigue in the CFS participants than the control groups was not supported. However, all three groups showed an increase in physical fatigue in the symptom focussing condition but no significant change in the distraction condition. This suggests that symptom-focusing does increase physical fatigue, for all adolescents, not only those with CFS. In contrast, for mental fatigue and pain there was no difference between symptom-focusing and distraction conditions. Regardless of

condition, the CFS participants showed an increase in both mental fatigue and pain, the asthma groups showed an increase in mental fatigue whereas the healthy controls showed no significant change over time. The findings suggest that for participants with CFS, tasks that require concentration on either symptoms or mental images are associated with an increase in mental fatigue. This finding is not necessarily surprising given clinical reports that concentrating is tiring for individuals with CFS. However, it is unclear why the asthma participants also show an increase in mental fatigue regardless of condition whereas the healthy individuals do not.

Pre-performance expectations & anxiety

It is likely that the adolescents with CFS have experienced a period of time where due to their illness and symptoms they have not been able to achieve their goals. This may have contributed to beliefs that they could not overcome their illness, which in turn may have caused further distress and avoidance. The results from this study suggest that the adolescents with CFS have lower expectations of performance, perhaps because they feel they cannot achieve things to the level they once did. They are possibly attributing previous performance difficulties to their CFS. This seems particularly apparent in relation to the exercise and social performance tasks. Seemingly, exercise is a specific issue for adolescents with CFS. The lower expectations and higher levels of anxiety surrounding this task suggest that the adolescents expected that the exercise task would make them feel worse and this increased their anxiety and sense that they would not perform well on the task. The CFS group were significantly more anxious prior to the social performance task than either of the other two groups. This may have been due to the parent-reported poor social skills. Social skills and anxiety require further research in adolescents with CFS.

Post-performance self-evaluations

The CFS participants performed more poorly than the other two groups on the social performance and exercise task. For the attention task they made no more errors but took longer than the control groups to complete the tasks. It was hypothesised that the discrepancy between self-evaluation of performance and objective ratings would be larger in the CFS group than either of the other two groups; their self-ratings would be more negative relative to objective ratings. This hypothesis was based on cognitive behavioural models which suggest that negative aspects of perfectionism are associated with critical performance self-evaluation (Shafran *et al.*, 2002). However, this prediction was not supported. For each of the three tasks, the CFS participants rated their performance significantly more negatively than the control groups. However, there was no evidence of a greater discrepancy between objective ratings and subjective ratings across the groups. Therefore the CFS participants appeared to be fairly accurately judging their level of performance. There was no evidence that they were being overly self-critical. This contrasts with Metzger and Denney (2002) reporting that CFS patients consistently underestimated their performance on a neuropsychological test when compared to healthy controls. Despite the lack of group difference in discrepancy between objective and subjective performance ratings, the lower absolute levels of performance in the CFS group may cause distress and contribute to their fatigue.

Misattribution of symptoms of stress

Participants in the two illness groups were asked to attribute increased physiological dysregulation as a result of the social performance task, to stress, illness, both, or other

factors. In the CFS group, the cognitive concepts – 'difficulty to think clearly' and 'difficulty finding the correct word' - were attributed significantly more to their illness rather than the stress of the task, when compared to the asthma group. This indicates a tendency to attribute symptoms to their illness rather than stress in a stressful situation. Wessely *et al.* (1989) proposed that this misattribution of symptoms to illness contributes to the development of negative illness beliefs and an avoidance of activities. It has been suggested in cognitive behavioural models of CFS in adults (Surarwy *et al.*, 1995), that this tendency to make somatic attributions is due to beliefs about negative emotions (stress) being unacceptable and a sign of weakness.

A lot of the young people with CFS as well as their mothers seem open to both psychological and physiological factors when attributing the cause of the CFS. Of course, the interaction between psychosocial factors and physical factors cannot be ignored clinically. There is a consensus that childhood trauma or other life events and chronic stressors might cause long-term impairment in terms of the ability to successfully adapt to stress, for example via disturbances to the HPA axis or autonomic dysregulation, thereby conveying a risk to developing CFS.

Maternal beliefs about the child's symptoms

Compared to mothers of adolescents with asthma, mothers of adolescents with CFS reported more negative beliefs about their child engaging in activity, more catastrophic beliefs about their child's symptoms, damage beliefs, and higher levels of all or nothing behaviour and avoidance of activity in their child. The cognitive behavioural models of CFS suggest these constructs may act to maintain CFS (e.g. (Surarwy *et al.*, 1995; Wessely *et al.*, 1989)). All questionnaire subscales about symptom beliefs completed by the child and their mother correlated. It is possible that beliefs in the mother may

influence the formation of beliefs in the child. In addition maternal distress may be associated with these sets of beliefs and attitudes in the parent which may influence the management of the child's illness. Thus, identifying psychological issues in mothers when considering and planning a child's treatment may facilitate the success of treatment overall. This was true of maternal depressive symptoms and treatment adherence to asthma therapy in inner-city children (Bartlett *et al.*, 2004).

Lower parental expectations about performance

In this study, on all tasks, parents of adolescents with CFS predicted that their children would find the performance tasks significantly more difficult, have higher levels of mental and physical fatigue and anxiety than the parents in the other two groups rated their child. On the social performance task and the exercise task, the parents of adolescents with CFS also reported that their child would perform significantly worse than the other two groups. These lower expectations could result in worse performance in the child due to less being expected of them. The adolescents with CFS also reported that their parents had significantly lower expectations of them than the healthy controls on the Frost perfectionism measure (FMPS). It is possible that parental expectations for performance have subsided since the onset of their child's condition, in line with their decrease in ability to complete activities. Fry and Martin (1996) reported that adolescents and their parents both under-estimated the adolescent's current activity levels, which perhaps ties in with lower perceived expectations from CFS parents in this current study. These lower expectations may contribute to the adolescents' avoidance of activity as the lower expectations may arise in conjunction with parental concerns about the illness which increases a focus on the condition.

Surprising findings

Having discussed all of the key findings, it seems poignant to also have a brief paragraph acknowledging the surprising findings that emerged during these studies in one focused area.

The most surprising findings are those scales where there was an absence of evidence, with the non-significant findings not fitting the hypothesised model. For instance, in the cross-sectional study, there was not a significant difference between the groups on overall perfectionism, or the subscales (excluding lower parental expectations and higher doubts about actions). Cognitive behavioural models of CFS propose that perfectionism leads to increased fatigue and disability through a rigorous attempt to meet high standards (Surarwy *et al.*, 1995). Here, it appears that perhaps these hypothesised factors are not as relevant in this adolescent population as was hypothesised. A failure to meet these perfectionist standards leads to increased effort, which subsequently leads to exhaustion and increased levels of fatigue (Deary & Chalder, 2010). As has already been discussed in this thesis, perfectionism as a construct is not well understood in this population so it remains possible that the adolescents are not aware of their propensity for expressing perfectionist tendencies. This warrants further investigation as this was the first study to investigate perfectionism in this adolescent population.

Equally surprising, contrary to hypotheses, there was not a significant difference between the groups on unhelpful beliefs about emotions in the cross-sectional study. Unhelpful beliefs about emotions at time 1 were also not a significant predictor of fatigue, physical functioning or school and social adjustment at time 2 in adolescents with CFS. It has been theorised that unhelpful beliefs about emotions or negative thoughts about expressing emotions would be important in CFS as a failure to

acknowledge emotions is thought to contribute to levels of fatigue. Seemingly in adolescents this was not the case. This was the first study in adolescent CFS to investigate unhelpful beliefs about emotions. Further studies are warranted. It may be possible to understand this construct further through the use of focus groups to qualitatively enquire as to patients' beliefs about the expression of emotions. Indeed, it is also possible that this construct is not as pertinent as was hypothesised. These unexpected findings are two of the findings that suggest areas where the CFS population may be largely comparable to the control groups.

Trans-diagnostic processes

In the present study, as assessed by the Mini International Neuropsychiatric Interview (MINI), 13% of adolescents with CFS were found to have generalised anxiety disorder. Thirteen percent had major depressive disorder and 11% of adolescents with CFS were found to suffer recurrent depression. The suggestion of an overlap with CFS and anxiety and depression is not a new concept (Chalder *et al.*, 2003). To highlight, the embarrassment avoidance subscale of the CBRQ was significantly higher in the CFS group than the asthma group. However, when controlling for depression, the effect of these beliefs was no longer significant. This suggests that low mood may be accounting for some of these beliefs. Rather than looking at each disorder in isolation, future research should focus on psychopathological and transdiagnostic processes (Mansell *et al.*, 2009).

The results of this thesis have highlighted a number of processes such as stress vulnerability and neuroticism which have already been shown to play a role in other problems such as anxiety or depression. There is growing evidence that difficulty in

processing emotions is transdiagnostic; (e.g. (Ladouceur *et al.*, 2000; Surarwy *et al.*, 1995)), operating across psychiatric and physical illness. Similarly, most cognitive behavioural approaches highlight the importance of behavioural factors in maintaining different clinical conditions. It is important to consider this when attempting to construct valid explanatory models and treatment for different conditions (Coughlin Della Selva, 2006). Cognitive behavioural treatments for many problems, including CFS, include some behavioural experiments (e.g. exposure to gradually increasing activity or exercise) and cognitive restructuring.

An evidence based model of CFS in children and adolescents

A model integrating the findings from this thesis, the reviewed research, and adult and child models of CFS (Chalder *et al.*, 2002; Surarwy *et al.*, 1995; Wessely *et al.*, 1989) is now presented (figure 9.1, page 359). The model presented is a stress-diathesis model of CFS in young people (building on that presented in figure 1.1, page 68). It is theorised that young people who develop CFS are likely to be vulnerable to stress through a variety of possible factors. It is suggested that this pre-existing stress vulnerability interacts with precipitating factors in the aetiology of CFS in young people. Subsequently, perpetuating factors act to maintain the CFS.

Implications for treatment / clinical implications

The evidence suggests that there are several factors which interact and contribute to the development and perpetuation of CFS in adolescents. The results suggest that fatigue and associated symptoms are a result of a complex interplay of cognitions, beliefs, behaviours, physiology and social factors which have evolved over time. These factors

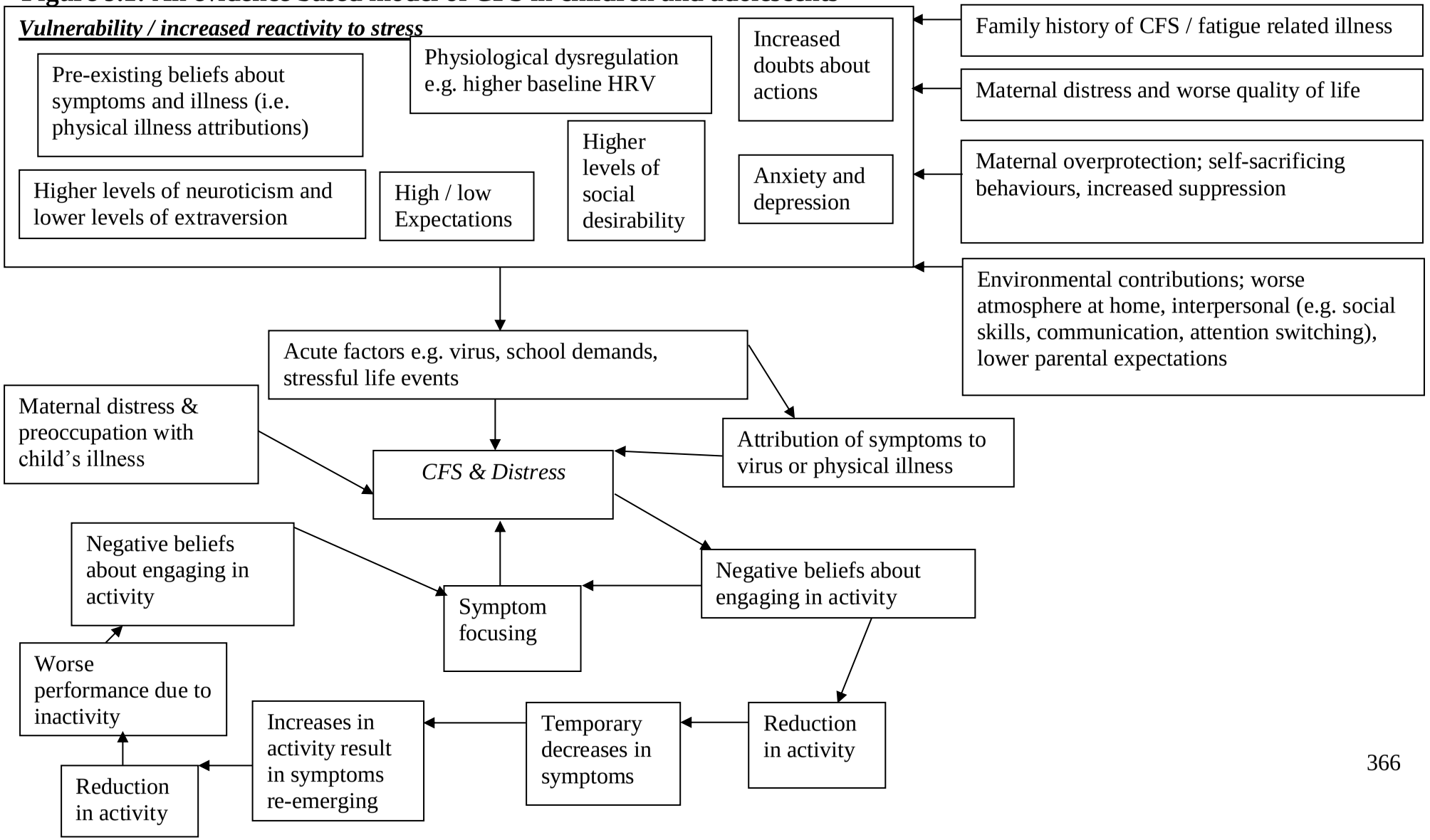
are typically addressed in family focused CBT (Chalder *et al.*, 2002). The proposed cognitive behavioural model of CFS (figure 9.1, page 359) illustrates how cognitive and behavioural responses may act to maintain CFS.

When co-morbid disorders are present these should be considered. For instance, an individual's mood usually improves as a graded return to activity and /or exercise is implemented. Patients with co-morbid anxiety disorders could benefit from learning about physiological responses to stress which may help address misattribution of symptoms to CFS rather than stress and help patients to address the stress itself. Treatment should be tailored to support specific personality types, and should address certain individual characteristics such as low self-esteem as well as higher levels of social desirability. Treatment should also be adjusted to take account of stressful life experiences where indicated.

Family focused CBT would certainly be recommended in this adolescent population given the finding that maternal distress is likely in many of these families. Of course children are dependent on their families during this developmental phase and so including the whole family would be important. Family focused CBT includes assisting the child and their family to make relevant changes which may involve a graded return to activity along with establishing a good sleep routine (Chalder *et al.*, 2002). The mother's beliefs about performance may also need to be addressed. As the child starts to do more it may be helpful to encourage the parent to modify their expectations of their child's ability. Approaches that challenge unhelpful cognitive and behavioural responses to symptoms may be important in improving the overall management of fatigue and disability in CFS. In adolescents it is likely that behaviour change and emotional support will prove to be the active ingredients of successful treatment. A

qualitative study of adolescent's perspectives on their treatment supports this notion (Dennison *et al.*, 2010).

Figure 9.1: An evidence based model of CFS in children and adolescents



Limitations of the thesis studies

Study limitations have already been discussed previously in the relevant chapters. All are considered in the sections below.

General limitations

Generalisation

This sample was recruited from two national specialist CFS services. Previous research has reported that CFS patients seen in tertiary clinics have a longer duration of CFS, more impairment in functioning and higher rates of co-morbidity than those not attending such services (Jason *et al.*, 2003). Given this, it is possible that the findings presented here are not generalisable to CFS patients within the community. At the same time, these patients were all seen at the outpatients departments and were presumably less severely affected by their CFS compared to those individuals who are housebound by their condition.

Type 1 error

A large number of comparisons in studies raise the possibility that some of the statistical significances are due to type 1 errors, so caution should be taken when interpreting the findings. A type 1 error would be the incorrect rejection of the null hypothesis (that no effect is observed). Bonferoni correction was used throughout to minimise this possible error. Avoidance of this error is possible when appropriate power is used to detect this difference and by keeping the number of comparisons to a

minimum. The number of participants in this group was appropriately powered to detect group differences on the different variables.

To avoid problems of multiple testing during the multiple regression models, the number of explanatory variables entered into a multiple regression model was limited to 1 variable per 10 participants, under statistical advice and following the univariate analyses, factors were only included in the model if they significantly predicted the fatigue at the $p < .10$ level (Field, 2005).

Interpretation of significant findings

It is important to note that even when associations do not reach statistical significance they may still be of clinical importance. These factors are alluded to in the relevant chapters, for instance, perfectionism or avoidance of activity in the prospective study. This is especially true for those factors which just miss reaching significance and they should not be ignored (Fukuda & Ohashi, 1997). CFS is a complex multifactorial condition, with different factors likely to be of varying degrees of importance across individuals.

The role of confounding variables

Confounders can be defined as independent explanatory factors that are associated with the exposure of interest and with the outcome of interest (Hennekens & Buring, 1987). They can obscure the true relationship between a risk factor and the outcome under study by leading to either over- or under-estimation of the association being tested if they are not taken account of in the design or statistical analysis stage. There were no

significant differences between groups on age, sex or ethnicity. IQ, depression and anxiety were controlled for in the analyses in this thesis as possible confounders. These were considered the key confounders which may possibly affect the outcomes. However, it is not always possible to know all of the variables that could possibly confound especially in the design and conduct of a study in a population not well understood. The previous literature was taken into account wherever possible.

Asthma comparison group

The asthma control group were selected as a chronic, physical illness comparison group. It was hypothesised that they would have scores that fell somewhere between the CFS group and the healthy control group. Only those who had not had acute asthma exacerbations within the last 2 months were included. Asthma was chosen as it can have a serious impact on individual's lives. However, their scores were actually very comparable to the healthy controls. Indeed, they reported almost 100% school attendance. This suggests that their illness was not having a significant impact on their functioning.

Although the asthma group were not as disabled by their symptoms as the CFS group, they may have had a diagnosis for longer. They will likely have had time to adjust to the diagnosis. In addition they were not dealing with an illness of unknown aetiology which makes adjusting potentially more difficult.

When reflecting on the asthma group as a chronic illness comparison group, it is possible that those participants recruited into this study were not representative of the more severely affected asthma group. However, all patients required daily medications to manage their symptoms, which was a standard criterion for severity.

Physiological equipment

There are some possible limitations to the psycho-physiological recordings. These are addressed in the discussions of chapter 6 (page 267) and chapter 7 (page 291).

Methodology

During the experimental tasks, participants were asked to complete the scales several times (before and after each task). It must be questioned whether the visual analogue scales (VAS) became repetitive by the end of the task session. It is possible that participants' completion of the VAS may have been affected by the repeated administration, for example tending to give the same responses each time. There was no evidence that this was the case. The exercise task detected a difference between groups and this was the final task. Also, participants were asked explicitly to complete them for how they were feeling right at that moment. It remains a factor that should be considered given this was a busy schedule with lots of form filling for the participants.

The asthma group and healthy control groups both had significant differences between the conditions in terms of how much time was spent on the symptom focusing vs. distraction task, focusing significantly less on the distraction condition. It is possible that the results reflected this. There were no differences in the time spent on these tasks between the condition groups within the CFS sample. As recommended by the task design, the researcher (author) left the room for the duration of the task, but it might be worth considering the advantages of staying in the room to ensure that the task is completed effectively and whether this would outweigh the possible distraction this could cause.

Future directions

The investigation of pathophysiology of CFS is in its infancy and future research would investigate this further using different experimental paradigms. It may be useful to measure physiology at home in the participant's natural environment, although differences in physiological responsivity to stress remains an important avenue to pursue. Future research could perhaps investigate whether focusing on specific symptoms makes more of a difference than others. Stahl, Rimes & Chalder (2014) investigated mediators of CBT treatment for CFS in adults. This study supported the notion that cognitive factors (including symptom focusing) mediated the effect of CBT.

The efficacy of graded exercise therapy should be investigated in future trials. Completing exercise tasks during treatment sessions, even during CBT may be a useful way to measure fear associated with exercise as well as performance itself.

Conclusions

This study found evidence to support the importance of constructs proposed in cognitive behavioural models of CFS such as negative beliefs about engaging in activity, symptom-focusing and unhelpful behaviours such as avoidance or all-or-nothing responses. These constructs are emphasised as central in the perpetuation of CFS in adolescents as they contribute to excessive resting, deconditioning and functional impairment. These factors are also theorised to add to intensified symptom experience and presumed severity. These factors need to be a key focus of treatment of CFS in adolescents and this study is the first to systematically assess such constructs in this population compared to healthy and illness control participants. Higher scores of

neuroticism, social desirability, doubts about actions as well as anxiety and depression, were observed in the adolescents with CFS and a significantly worse quality of life. Each of these factors is presented in the proposed updated model of adolescent CFS (figure 9.1, page 359). Maternal distress may be associated with the predisposition of CFS in adolescents. This provides a better clinical picture of the mothers in this patient group as well as the family environment and the mother's responses to the child's illness.

This evidence calls for a family approach to assessment and management (Chalder *et al.*, 2002). The thesis discusses which factors need to be tackled in the context of individually tailored, family-focused CBT and inform future intervention. Further investigation into this adolescent population with CFS and treatment studies based on this hypothesised model is recommended.

Reference List

Abdel-Khalek, A. M. (2004). Prevalence of reported insomnia and its consequences in a survey of 5,044 adolescents in Kuwait. *Sleep, 27*, 726-731.

Afari, N., Schmaling, K., Herrall, R., Ashton, S., Goldberg, J., & Buchwald, D. S. (2000). Coping strategies in twins with chronic fatigue and chronic fatigue syndrome. *Journal of Psychosomatic Research, 48*, 547-554.

Alisky, J. M., Iczkowski, K. A., & Foti, A. A. (1991). Chronic Fatigue Syndrome. (Letter). *American Family Physician, 44*, 56-57.

Antony, M. M., & Swinson, R. P. (1998). *When Perfect Isn't Good Enough: Strategies for Coping with Perfectionism*: New Harbinger Publications Incorporated.

Arnow, B. (2004). Relationships between childhood maltreatment, adult health and psychiatric outcomes, and medical utilization. *Journal of Clinical Psychiatry, 65 (supplement)*(12), 10-15.

Axell, A.-M., MacLean, H. E., Plant, D. R., Harcourt, L. J., Davis, J. A., Jimenez, M., . . . Zajac, J. D. (2006). Continuous testosterone administration prevents skeletal muscle atrophy and enhances resistance to fatigue in orchidectomized male mice. *American Journal of Physiology - Endocrinology and Metabolism, 291*, E506-E516.

Babson, A. L. (2005). Unitized Reagent Random Access Analyzers: IMMULITE and IMMULITE 1000. In D. Wild (Ed.), *The Immunoassay Handbook* (pp. 370-373): Elsevier Ltd.

Bandura, A. (1977). *Social Learning Theory*. Englewood Cliffs, NJ: Prentice Hall.

Bandura, A., Barbaranelli, C., Caprara, G. V., & Passtorelli, C. (1996). Multifaceted Impact of Self-Efficacy Beliefs on Academic Functioning. *Child Development, 67*(3), 1206-1222.

Baron-Cohen, S., Wheelwright, S., Skinner, R., Martin, J., & Clubley, E. (2001). The autism-spectrum quotient (AQ): evidence from Asperger syndrome/high-functioning autism, males and females, scientists and mathematicians. *Journal of Autism and Developmental Disorders, 31*, 5-17.

Bartlett, S. J., Krishnan, J. A., Riekert, K. A., Butz, A. M., Malveaux, F. J., & Rand, C. S. (2004). Maternal depressive symptoms and adherence to therapy in inner-city children with asthma. *Pediatrics, 113*(2), 229-237.

Baumrind, D. (1971). Current patterns of parental authority. *Developmental Psychology Monograph, 4*, 1-103.

Baumrind, D. (1991). The influence of parenting style on adolescent competence and substance use. *Journal of Early Adolescence, 11*, 56-95.

Bech, P. (1998). *Quality of life in the psychiatric patient*. London: Mosby-Wolfe.

Bech, P. (2001). Male depression: stress and aggression as pathways to major depression. In D. A. a. T. A (Ed.), *Depression: Social and economic timebomb* (pp. 63-66). London: BMJ Books.

Beck, A. T., Ward, C. H., Mendleson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. *Archives of General Psychiatry, 4*, 561-571.

Beesdo, K., Knappe, S., & Pine, D. S. (2009). Anxiety and Anxiety Disorders in Children and Adolescents: Developmental Issues and Implications for DMS-V. *Psychiatric Clinics of North America, 32*(3), 483-524.

Beidel, D. C., Turner, S. M., & Morris, T. L. (1995). A new inventory to assess social anxiety and phobia: The Social Phobia and Anxiety Inventory for Children. . *Psychological Assessment, 7*, 73-79.

Reference List

Bell, D. S., Bell, K. M., & Cheney, P. R. (1994). Primary juvenile fibromyalgia syndrome and Chronic Fatigue Syndrome in adolescents. *Clinical Infectious Diseases, 18*(1), 21-23.

Bell, D. S., Jordan, K., & Robinson, M. (2001). Thirteen-year follow-up of children and adolescents with chronic fatigue syndrome. *Pediatrics, 107*, 994-998.

Bell, K. M., Cookfair, D., Bell, D. S., Reese, P., & Cooper, L. (1991). Risk factors associated with chronic fatigue syndrome in a cluster of pediatric cases. *Review of Infectious Diseases, 13*(1), S32-38.

Benditt, D. G., Ferguson, D. W., Grubb, B. P., Kapoor, W. N., Kugler, J., Lerman, B. B., . . . Wood, D. L. (1996). Tilt table testing for assessing syncope. *Journal American College of Cardiologists, 28*, 263-275.

Bernstein, D., & Fink, L. (1998). *Childhood Trauma Questionnaire: A retrospective self-report*: San Antonio, TX: The Psychological Corporation.

Bialek, M., Zaremba, P., Borowicz, K. K., & Czuczwar, S. J. (2004). Neuroprotective role of testosterone in the nervous system. *Polish Journal of Pharmacology, 56*(5), 509-518.

Bogels, S. M., & Brechman-Toussaint, M. L. (2006). Family issues in child anxiety: Attachment, family functioning, parental rearing and beliefs. *Clinical Psychology Review, 26*(2006), 834-856.

Bolger, N. (1990). Coping as a personality process: A prospective study. *Journal of Personality and social psychology, 39*, 525-537.

Bolger, N., & Schilling, E. A. (1991). Personality and problems of everyday life: The role of neuroticism in exposure and reactivity to daily stressors. *Journal of Personality, 59*, 356-386.

Boucsein, W. (1992). *Electrodermal activity*: New York: Plenum Press.

Bould, H., Collin, S. M., Lewis, G., Rimes, K., & Crawley, E. (2013). Depression in paediatric chronic fatigue syndrome. *Archive of Disease in Childhood, 98*, 425-428.

Boyle, M. H., & Pickles, A. (1997a). Influence of maternal depressive symptoms on ratings of childhood behaviour. *Journal of Abnormal Child Psychology, 25*(5), 399-412.

Boyle, M. H., & Pickles, A. (1997b). Maternal depressive symptoms and ratings of emotional disorder symptoms in children and adolescents. *The Journal of Child Psychology and Psychiatry and Allied Disciplines, 38*(8), 981-992.

Brace, M. J., Smith, M. S., McCauley, E., & Sherry, D. D. (2000). Family Reinforcement of Illness Behaviour: A Comparison of Adolescents with Chronic Fatigue Syndrome, Juvenile Arthritis, and Healthy Controls. *Developmental and Behavioural Pediatrics, 21*(5), 332-339.

Brignole, M., Alboni, P., Benditt, D., Bergfeldt, L., Blanc, J. J., Bloch Thomsen, P. E., . . . for the Task Force on Syncope, E. S. o. C. (2001). Guidelines on management (diagnosis and treatment) of syncope. *European Heart Journal, 22*, 1256–1306.

Brockett, D. (2002). Location Sound: The Basics and Beyond. from http://www.kenstone.net/fcp_homepage/location_sound.html

Brown, E. J., Heimberg, R. G., Frost, R. O., Makris, G. S., Juster, H. R., & Leung, A. W. (1999). Relationship of perfectionism to affect, expectations, attributions and performance in the classroom. *Journal of Social and Clinical Psychology, 18*(1), 98-120.

Browne, T., & Chalder, T. (2006). Chronic Fatigue Syndrome. *Psychiatry, 5*(2), 48-51.

Buchwald, D. S., Rea, T. D., Katon, W. J., Russo, J. E., & Ashley, R. L. (2000). Acute infectious mononucleosis: characteristics of patients who report failure to recover. *American Journal of Medicine, 109*, 531-537.

Carter, B. D., Edwards, J. F., Kronenberger, W. G., Michalczyk, L., & Marshall, G. S. (1995). Case Control Study of Chronic Fatigue in Pediatric Patients. *Pediatrics, 95*, 179-186.

Carver, C. (1978). A Cybernetic Model of Self-Attention Processes. *Journal of Personality and social psychology, 37*, 1251-1281.

Caseras, X., Mataix-Cols, D., Rimes, K. A., Giampietro, V., Brammer, M., Zelaya, F., . . . Godfrey, E. (2008). The neural correlates of fatigue: an exploratory imaginal fatigue provocation study in chronic fatigue syndrome. *Psychological Medicine, 38*, 941-951.

Caspi, A. (1998). *Handbook of Child Psychology: volume 3. Social, emotional and personality development* (Vol. 5): *New York: Wiley*.

Cella, M., & Chalder, T. (2010). Measuring fatigue in clinical and community settings. *Journal of Psychosomatic Research, 69*, 17-22.

Cella, M., Sharpe, M., & Chalder, T. (2011). Measuring disability in patients with chronic fatigue syndrome: reliability and validity of the Work and Social Adjustment Scale. *Journal of Psychosomatic Research, 71*(3), 124-128.

Chalder, Tong, J., & Deary, V. (2002). Family focused cognitive behaviour therapy for chronic fatigue syndrome in adolescents. *Archives of Disease in Childhood, 86*, 95-97.

Chalder, T. (2012). [Personal Communication].

Chalder, T., Berlowitz, G., Pawlikowska, T., Watts, L., Wessely, S., Wright, D., & Wallace, E. P. (1993). Development of a fatigue scale. *Journal of Psychosomatic Research, 37*(2), 147-153.

Chalder, T., Deary, V., Husain, K., & Walwyn, R. (2010). Family-focused cognitive behaviour therapy versus psycho-education for Chronic Fatigue Syndrome in 11- to 18-year-olds: a randomized controlled treatment trial. *Psychological Medicine, 40*, 1269-1279.

Chalder, T., Goodman, R., Wessely, S., Hotopf, M., & Meltzer, H. (2003). Epidemiology of chronic fatigue syndrome and self-reported myalgic encephalomyelitis in 5-15 year olds: cross-sectional study. *British Medical Journal, 327*, 654-655.

Cho, H. J., Skowera, A., Cleare, A., & Wessely, S. (2006). Chronic Fatigue Syndrome: an update focusing on phenomenology & pathophysiology. *Personality disorders and neuroses, 19*, 67-73.

Claustrat, B., Brun, J., & Chazot, G. (2005). The basic physiology and pathophysiology of melatonin. *Sleep Medicine Reviews, 9*(1), 11-24.

Cleare, A. J. (2003). The HPA axis and the genesis of chronic fatigue syndrome. *Trends in Endocrinology & Metabolism, 15*(2), 55-59.

Coddington, A., & Chalder, T. (2003). *Do parents of children with CFS have higher expectations of them?* Paper presented at the British Association of Behavioural and Cognitive Psychotherapists Annual Conference, York.

Cohen, H., Neumann, L., Shore, M., Amir, M., Cassuto, Y., & Buskila, D. (2000). Autonomic dysfunction in patients with fibromyalgia: application of power spectral analysis of heart rate variability. *Seminars in Arthritis and Rheumatism, 29*(4), 217-227.

Cohen, L. H., Burt, C. E., & Bjorck, J. P. (1987). Life stress and adjustment: Effects of life events experienced by young adolescents and their parents. *Developmental Psychology, 23*, 583-592.

Cohen, P., Cohen, J., Kasen, S., Velez, C. N., Hartmark, C., Johnson, J., . . . Streuning, E. L. (1993). An epidemiological study of disorders in late childhood and

adolescence - age and gender specific prevalence. *The Journal of Child Psychology and Psychaitry, 34*(6), 851-867.

Cordingley, L., Wearden, A., Appleby, L., & Fisher, L. (2001). The Family Response Questionnaire: A new scale to assess the responses of family members to people with chronic fatigue syndrome. *Journal of Psychosomatic Research, 51*(2), 417-424.

Costello, E. J., Egger, H. L., & Angold, A. (2005). The developmental epidemiology of anxiety disorders: phenomenology, prevalence and comorbidity. *Child and Adolescent Psychiatry, 14*(4), 631-645.

Coughlin Della Selva, P. (2006). Emotional processing in the treatment of psychosomatic disorders. *Journal of Clinical Psychology, In Session*(April).

Crandall, V. C., Crandall, V. J., & Katkovsky, W. (1965). A children's social desirability questionnaire. *Journal of Consulting Psychology, 29*, 27-36.

Crawley, E., Emond, A. M., & Sterne, J. A. C. (2011). Unidentified Chronic Fatigue Syndrome / Myalgic Encephalomyelitis (CFS/ME) is a major cause of school absence: surveillance outcomes from school-based clinics. *British Medical Journal Open, 1*(2), E000252.

Crawley, E., Hunt, L., & Stallard, P. (2009). Anxiety in childrenwith CFS/ME. *European Child and Adolescent Psychiatry, 18*, 683-689.

Crawley, E., & Sterne, J. A. C. (2009). Association between school absence and physical function in paediatric chronic fatigue syndrome/myalgic encephalopathy. *Archive of Disease in Childhood, 94*, 752-756.

Cresswell, C., Schniering, C. A., & Rapee, R. M. (2005). Threat interpretation in anxious children and their mothers: comparison with nonclinical children and the effects of treatment. *Behaviour, Research and Therapy, 43*(10), 1375-1381.

Csuka, M., & McCarty, D. J. (1985). Simple method for measurement of lower extremity muscle strength. *American Journal of Medicine, 78*(1), 77-81.

Cyranowski, J. M., Frank, E., Young, E., & Shear, K. (2000). Adolescent onset of the gender difference in lifetime rates of major depression. A theoretical model. *Archives of General Psychiatry, 57*(1), 21-27.

Darling, N., & Steinberg, L. (1993). Parenting Style as Context: An Integrative Model. *Psychological Bulletin, 113*(3), 487-496.

Davis-Kean, P. E., Vida, M., & Eccles, J. (2001). *Influences on Parental Expectations for Post-High School Transitions*. Paper presented at the Society for Research on Child Development Biennial Conference, Minneapolis, MN.

Dawson, M. E., Schell, A. M., & Filion, D. L. (2007). *The electrodermal system* (L. G. T. a. G. G. B. J. T. Cacioppo Ed.): Cambridge University Press: USA.

de Wit, M., Pouwer, F., Gemke, R. J., Delemarre-van de Waal, H. A., & Snoek, F. J. (2007). Validation of the WHO-5 Well-Being Index in adolescents with type 1 diabetes. *Diabetes Care, 30*(8), 2003-2006.

Deale, A., Chalder, T., & Wessely, S. (1998). Illness beliefs and treatment outcome in chronic fatigue syndrome. *Journal of Psychosomatic Research, 45*(1), 77-83.

Deary, V., & Chalder, T. (2010). Personality and perfectionism in chronic fatigue syndrome: a closer look. *Psychology and Health, 25*, 465-475.

DeLuca, J., Johnson, S. K., Ellis, S. P., & Natelson, B. H. (1997). Sudden vs. gradual onset of chronic fatigue syndrome differentiates individuals on cognitive and psychiatric measures. *Journal of Psychiatric Research, 31*, 83-90.

Demitrack, M., Dale, J., Straus, S., Lawe, L., Listwak, S. J., Kruesi, M. J., . . . Gold, P. W. (1991). Evidence for impaired activation of the hypothalamic pituitary adrenal axis inpatients with chronic fatigue syndrome. *Journal of Clinical Endocrinology and Metabolism, 73*, 1224-1234.

Dennison, L., Stanbrook, R., Moss-Morris, R., Yardley, L., & Chalder, T. (2010). Cognitive behavioural therapy and psycho-education for chronic fatigue syndrome in young people: Reflections from the families' perspective. *British Journal of Health Psychology, 15*(1), 167-183.

Dinos, S., Khoshaba, B., Ashby, D., White, P. D., Nazroo, J., & Wessely, S. (2009). A systematic review of chronic fatigue, its syndromes and ethnicity: prevalence, severity, co-morbidity and coping. *International Journal of Epidemiology, 38*, 1554-1570.

Dixon, M. J., Harrigan, K. A., Sandhu, R., Collins, K., & Fugelsang, J. A. (2010). Losses disguised as wins in modern multi-line video slot machines. *Addiction*, 1-6.

Dobbins, J. G., Reyes, M., Cole, N., Steel, P. L., Randall, B., & Reeves, W. C. (1997). The natural history of CFS in the CDC Surveillance System. *Journal of Chronic Fatigue Syndrome, 3*, 132-133.

Downey, G., & Coyne, J. C. (1990). Children of Depressed Parents: An Integrative Review. *Psychological Bulletin, 108*(1), 50-76.

Dowsett, E. G., & Colby, J. (1997). Long term sickness absence due tor ME/CFS in UK Schools: An epidemiological study with medical and educational implications. *Journal of Chronic Fatigue Syndrome, 3*(2), 29-42.

Duggan, C., Sham., P., Lee, A., Minne, C., & Murray, R. (1995). Neuroticism: a vulnerability marker for depression evidence from a family study. *Journal of Affective Disorders, 35*(3), 139-143.

Eminson, D. M. (2007). Medically unexplained symptoms in children and adolescents *Clinical Psychology Review, 27*, 855-871.

Eriksen, B. A., & Eriksen, C. W. (1974). Effects of noise letters upon identification of a target letter in a non- search task. *Perception and Psychophysics, 16*, 143-149.

Eysenck, S. B. G., Eysenck, H. J., & Barrett, P. (1985). A revised version of the psychoticism scale. *Personality and Individual Differences, 6*(1), 21-29.

Farmer, A., Fowler, T., Scourfield, J., & Thapar, A. (2004). Prevalence of chronic disabling fatigue in children and adolescents. *British Journal of Psychiatry, 184*, 477-481.

Farmer, A., Scourfield, J., Martin, N., Cardno, A., & McGuffin, P. (1999). Is disabling fatigue in childhood influenced by genes? *Psychological Medicine, 29*, 279-282.

Feder, H. M., Dworkin, P. H., & Orkin, C. (1994). Outcome of 48 pediatric patients with chronic fatigue. A clinical experience. *Archives of Family Medicine, 3*(12), 1049-1055.

Fekedulegn, D. B., Andrew, M. E., Burchfiel, C. M., Violanti, J. M., Hartley, T. A., Charles, L. E., & Millar, D. B. (2007). Area under the curve and other summary indicators of repeated waking cortisol measurements. *Psychosomatic Medicine, 69*(7), 651-659.

Field, A. (2005). *Discovering statistics using SPSS* (D. B. Wright Ed. 2nd ed.). London: SAGE Publications.

Figner, B., & Murphy, R. O. (2011). Using skin conductance in judgment and decision making research *A handbook of process tracing methods for decision research* (pp. 163-184): New York, NY: Psychology Press.

Fisher, H., & Crawley, E. M. (2012). Why do young people with CFS/ME feel anxious? A qualitative study. *Clinical Child Psychology and Psychiatry*, 1-18.

Fisher, L., & Chalder, T. (2003). Childhood experiences of illness and parenting in adults with Chronic Fatigue Syndrome. *Journal of Psychosomatic Research, 54*, 439-443.

Flett, G. L., Hewitt, P. L., Boucher, D. J., Davidson, L. A., & Munro, Y. (1997). *The child adolescent perfectionism scale: development, validation, and association with adjustment*.

Frost, R. O., Lahart, C. M., & Rosenblate, R. (1991). The development of perfectionism: A study of daughters and their parents. *Cognitive Therapy and Research, 15*, 469-489.

Frost, R. O., Marten, P., Lahart, C., & Rosenblate, R. (1990). The dimensions of perfectionism. *Cognitive Therapy and Research, 14*, 449-468.

Fry, A. M., & Martin, M. (1996). Cognitive idiosyncrasises among children with the Chronic Fatigue Syndrome: Anomalies in self-reported activity levels. *Journal of Psychosomatic Research, 41*(3), 213-223.

Fryers, T., Brugha, T., Morgan, Z., Smith, J., Hill, T., Carta, M., . . . Kovess, V. (2004). Prevalence of psychiatric disorder in Europe: the potential and reality of meta-analysis. *Social Psychiatry and Psychiatric Epidemiology, 39*(11), 899-905.

Fukuda, K., & Ohashi, Y. (1997). A guideline for reporting results of statistical analysis in Japanese Journal of Clinical Oncology. *Japanese Journal of Clinical Oncology, 27*(3), 121-127.

Fukuda, K., Straus, S. E., Hickie, I., Sharpe, M. C., Dobbins, J. G., & Komaroff, A. (1994). The Chronic Fatigue Syndrome: A comprehensive Approach to Its Definition and Study. *Annals of Internal Medicine, 121*(12), 953-959.

Gabella, G. (2001). Autonomic Nervous System. *eLS*.

Gaigg, S. B., & Bowler, D. M. (2007). Differential fear conditioning in Asperger's syndrome: Implications for an amygdala theory of autism. *Neuropsychologica, 45*, 2125-2134.

Gallagher, A. M., Thomas, J. M., Hamilton, W. T., & White, P. D. (2004). Incidence of fatigue symptoms and diagnoses presenting in UK family care from 1990 to 2001. *Journal of Royal Society of Medicine, 97*, 571-575.

Galland, B. C., Jackson, P. M., Sayers, R. M., & Taylor, B. J. (2008). A matched case-control study of orthostatic intolerance in children / adolescents with Chronic Fatigue Syndrome. *Pediatric Research, 63*(2), 1-7.

Garralda, E., & Rangel, L. (2001). Childhood Chronic Fatigue Syndrome. *American Journal of Psychiatry, 158*(7), 1161-1162.

Garralda, E., & Rangel, L. (2004). Impairment and coping in children and adolescents with chronic fatigue syndrome: a comparative study with other paediatric disorders. *Journal of Child Psychology and Psychiatry, 45*(3), 543-552.

Garralda, E., & Rangel, L. (2005). Chronic fatigue syndrome of childhood. Comparative study with emotional disorders. *European Child and Adolescent Psychiatry, 14*, 424-430.

Garralda, M. E., Rangel, L. A., Levin, M., & Roberts, H. (1999). Psychiatric adjustment in adolescents with a history of childhood chronic fatigue syndrome. *Journal of the American Academy of Child and Adolescent Psychiatry, 38*, 1515-1521.

Gerlsma, C., Arrindell, W. A., Van der Veen, N., & Emmelkamp, P. M. G. (1991). A parental rearing style questionnaire for use with adolescents: Psychometric evaluation of the EMBU-A. *Personality and Individual Differences, 12*, 1245-1253.

Gill, T. M., Williams, C. S., & Tinetti, M. E. (1995). Assessing risk for the onset of functional dependence among older adults: the role of physical performance. *Journal of American Geriatric Society, 43*(6), 603-609.

Godfrey, E., Cleare, A., Coddington, A., Roberts, A., Weinman, J., & Chalder, T. (2009). Chronic Fatigue Syndrome in adolescents: do parental expectations of

their child's intellectual ability match the child's ability? *Journal of Psychosomatic Research, 67*(2), 165-168.

Goldberg, D. (1972). *The detection of psychiatric illness by questionnaire: A technique for the identification and assessment of non-psychotic psychiatric illness*: London, New York: Oxford University Press.

Goldberg, D. P., Gater, R., Sartorius, N., Ustun, T. B., Piccinelli, M., & Gureje, O. R., C. (1997). The validity of two versions of the GHQ in the WHO study of mental illnesses in general health care. *Psychological Medicine, 27*(1), 191-197.

Goldberg, D. P., & Hillier, V. F. (1979). A scaled version of the General Health Questionnaire. *Psychological Medicine, 9*, 139-145.

Goldberg, D. P., & Williams, P. (1988). *A user's guide to the General Health Questionnaire*: Windsor, UK: NFER-Nelson.

Goodwin, L., White, P. D., Hotopf, M., Stansfield, S. A., & Clark, C. (2011). Psychopathology and physical activity as predictors of Chronic Fatigue Syndrome in the 1958 British birth cohort: A replication study of the 1946 and 1970 birth cohorts. *Annals of Epidemiology, 21*(5), 343-350.

Gordon, B., & Lubitz, L. (2009). Promising outcomes of an adolescent Chronic Fatigue Syndrome inpatient programme. *Journal of Pediatrics and Child Health, 45*, 286-290.

Gordon, B. A., Knapman, L. M., & Lubitz, L. (2010). Graduated exercise training and progressive resistance training in adolescents with Chronic Fatigue Syndrome: a randomised controlled pilot study. *Clinical Rehabilitation, 24*(10), 1072-1079.

Gray, S. E., & Rutter, D. R. (2007). Illness representations in young people with Chronic Fatigue Syndrome. *Psychology and Health, 22*(2), 159-174.

Haig-Ferguson, A., Tucker, P., Eaton, N., Hunt, L., & Crawley, E. (2009). Memory and attention problems in children with CFS/ME. *Archives of Disease in Childhood, 94*, 757-762.

Hambrook, D., Oldershaw, A., Rimes, K., Schmidt, U., Tchanturia, K., Treasure, J., . . . Chalder, T. (2011). Emotional expression, self-silencing, and distress tolerance in anorexia nervosa and chronic fatigue syndrome. *British Journal of Clinical Psychology, 50*(3), 310-325.

Hareide, L., Finset, A., & Wyller, V. B. (2011). Chronic Fatigue Syndrome: a qualitative investigation of young patient's beliefs and coping strategies. *Disability and Rehabilitation, 33*(23-24), 2255-2263.

Harris, J. R. (2011). *The nurture assumption: Why children turn out the way they do*: Free Press.

Harvey, A. G., Clark, D. M., Ehlers, A., & Rapee, R. M. (2000). Social anxiety and self-impression: Cognitive preparation enhances the beneficial effects of video feedback following a stressful social task. *Behaviour Research and Therapy, 38*, 1183-1192.

Harvey, S., Wadsworth, M., Wesseley, S., & Hotopf, M. (2008). Etiology of Chronic Fatigue Syndrome: Testing popular hypotheses using a national birth cohort study. *Psychosomatic Medicine, 70*, 488-495.

Hayes, S. C., Strosahl, K., & Wilson, K. G. (1999). *Acceptance and Commitment Therapy: An experiential approach to behaviour change*: New York: Guilford Press.

Heim, C., Nater, U. M., Maloney, E., Boneva, R., Jones, J. F., & Reeves, W. C. (2009). Childhood Trauma and Risk for Chronic Fatigue Syndrome. *Archives of General Psychiatry, 66*(1), 72-78.

Heim, C., Wagner, D., Maloney, E., Papanicolaou, D. A., Solomon, L., Jones, J. F., . . . Reeves, W. C. (2006). Early Adverse Experience and Risk for Chronic Fatigue Syndrome. *Archives of General Psychiatry, 63*, 1258-1266.

Hennekens, C. H., & Buring, J. E. (1987). *Epidemiology in Medicine*: Lippincott Williams & Wilkins.

Hofmann, S. G., & Kashdan, T. B. (2010). The Affective Style Questionnaire: Development and psychometric properties. *Journal of Psychopathology and Behavioral Assessment, 32*, 255-263.

Hollender, M. H. (1965). Perfectionism. *Comprehensive Psychiatry, 6*, 94-103.

Holmes, G. P., Kaplan, J. E., Gantz, N. M., Komaroff, A. L., Schonberger, L. B., Straus, S. E., . . . Brus, I. (1988). Chronic Fatigue Syndrome: A working case definition. *Annals of International Medicine, 108*, 387-389.

Hotopf, M., Carr, S., Mayou, R., Wadsworth, M., & Wessely, S. (1997). Why do children have chronic abdominal pain, and what happens to them when they grow up? Population based cohort study. *British Medical Journal, 317*(7139), 1196-1200.

Huang, Y., Katz, B. Z., Mears, C., Kielhofner, G. W., & Taylor, R. (2010). Postinfectious fatigue in adolescents and physical activity. *Archives of Pediatric and Adolescent Medicine, 164*(9), 803-809.

Hurum, H., Sulheim, D., Thaulow, E., & Wyller, V. B. (2011). Elevated nocturnal blood presure and heart rate in adolescent chronic fatigue syndrome. *Acta Pediatrica: Nurturing the Child, 100*, 289-292.

Jack, D. C. (1991). *Silencing the self: women and depression*. Cambridge: Harvard University Press.

Janig, W. (1989). Autonomic Nervous System. *Human Physiology*, 333-370.

Jason, L., Melrose, H., Lerman, A., Burroughs, V., Lewis, K., King, C., & Frankenberry, E. (1999a). Managing chronic fatigue syndrome: Overview and case study. *American Association of Occupational Health Nurses Journal, 47*, 17-21.

Jason, L. A., Jordan, K., Miike, T., Bell, D. S., Lapp, C., Torres-Harding, S., . . . Van Hoof, E. L. S. (2006). A pediatric case definition for myalgic encephalomyelitis and chronic fatigue syndrome. *Journal of Chronic Fatigue Syndrome, 13*(2-3), 1-44.

Jason, L. A., Richman, J. A., Rademaker, A. W., Jordan, K. M., Plioplys, A. V., Taylor, R. R., . . . Plioplys, S. (1999b). A community-based study of chronic fatigue syndrome. *Archives of International Medicine, 159*(2), 129-137.

Jason, L. A., Witter, E., & Torress-Harding, S. (2003). Chronic fatigue syndrome, coping, optimism and social support. *Journal of Mental Health, 12*(2), 109-118.

Jelbert, R., Stedmon, J., & Stephens, A. (2010). A qualitative exploration of adolescents/ experiences of Chronic Fatigue Syndrome. *Clinical Child Psychology and Psychiatry, 15*(2), 267-283.

Jones, J. F., Nisenbaum, R., Solomon, L., Reyes, M., & Reeves, W. C. (2004). Chronic Fatigue Syndrome and Other Fatiguing Illnesses in Adolescents: A Population-based Study. *Journal of Adolescent Health, 35*, 34-40.

Jordan, K. M., Ayers, P. M., Jahn, S. C., Taylor, K. K., Huang, C. F., Richman, J., & Jason, L. A. (2000). Prevalence of fatigue and chronic fatigue syndrome-like illness in children and adolescents. *Journal of Chronic Fatigue Syndrome, 6*, 3-21.

Jordan, K. M., Huang, C.-F., & Jason, L. A. (2006). Prevalence of pediatric chronic fatigue syndrome in a community based sample. *Journal of Chronic Fatigue Syndrome, 13*(2-3), 75-78.

Jordan, K. M., Landis, D. A., Downey, M. C., Osterman, S. L., Thurm, A. E., & Jason, L. A. (1998). Chronic Fatigue Syndrome in Children and Adolescents: A Review. *Journal of Adolescent Health, 22*, 4-18.

Kagan, J., Snidman, N., Arcus, D., & Reznick, J. S. (1994). *Galen's prophecy: Temperament in human nature*: Basic Books, New York.

Kaplan, D., Liu, X., & Kaplan, H. (2001). Influence of parents' self-feelings and expectations on children's academic performance. *The Journal of Educational Research, 94*, 360-370.

Kato, K., Sullivan, P. F., Evengard, B., & Pedersen, N. L. (2006). Premorbid Predictors of Chronic Fatigue. *Archives of General Psychiatry, 63*, 1267-1272.

Katz, B. Z., Shirasishi, Y., Mears, C. J., Binns, H. J., & Taylor, R. (2009). Chronic Fatigue Syndrome After Infectious Mononucleosis in Adolescents. *Pediatrics, 124*(1), 189-193.

Katz, B. Z., Stewart, J. M., Shiraishi, Y., Mears, C. J., & Taylor, R. (2012). Orthostatic Tolerance Testing in a Prospective Cohort of Adolescents With Chronic Fatigue Syndrome and Recovered Controls Following Infectious Mononucleosis. *Clinical Pediatrics, 51*(9), 835-839.

Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., . . . Ryan, N. (1997). Schedule for affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): Initial Reliability and Validity Data. *Journal of American Academy of Child and Adolescent Psychiatry, 36*(7), 1099-1107.

Kavelaars, A., Kuis, W., Knook, L., Sinnema, G., & Heijnen, C. J. (2000). Disturbed Neuroendocrine-Immue Interactions in Chronic Fatigue Syndrome. *The Journal of Clinical Endocrinology and Metabolism, 85*(2), 692-696.

Kawatani, J., Mizuno, K., Shiraishi, S., Takao, M., Joudoi, T., Fukuda, S., . . . Tomoda, A. (2011). Cognitive dysfunction and mental fatigue in childhood chronic fatigue syndrome - a 6 month follow-up study. *Brain and Development, 33*(10), 832-841.

Kemp, A. H., Quintana, D. S., Felmingham, K. L., Matthews, S., & Jelinek, H. F. (2012). Depression, comorbid anxiety disorders, and heart rate variability in physically healthy, unmedicated patients: implications for cardiovascular risk. *PLoS ONE, 7*, E30777.

Kempke, S., Luyten, P., Claes, S., Van Wambeke, P., Bekaert, P., Goossens, L., & Van Houdenhove, B. (2013). The prevalence and impact of early childhood trauma in Chronic Fatigue Syndrome. *Journal of Psychiatric Research, 47*, 664-669.

Kennedy, G., Khan, F., Hill, A., Underwood, C., & Belch, J. J. F. (2010). Biochemical and Vascular Aspects of Pediatric Chronic Fatigue Syndrome. *Archives of Pediatric and Adolescent Medicine, 164*(9), 817-823.

Kennedy, G., Spence, V. A., McLaren, M., Hill, A., Underwood, C., & Belch, J. J. F. (2005). Oxidative stress levels are raised in chronic fatigue syndrome and are associated with clinical symptoms. *Free Radical Biology & Medicine, 39*, 584-589.

Kennedy, G., Underwood, C., & Belch, J. J. F. (2010a). Physical and functional impact of Chronic Fatigue Syndrome / Myalgic Encephalomyelitis in childhood. *Pediatrics, 125*, 1324-1330.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry, 62*(6), 593-602.

Kim, D. H., Kweon, T. D., Nam, S. B., Han, D. W., Y., C. W., & Lee, J. S. (2008). Effects of target concentration infusion of propofol and tracheal intubation on QTc interval. *Anaesthesia, 63*, 1061-1064.

Kirschbaum, C., Pirke, K., & Hellhammer, D. H. (1995). Preliminary evidence for reduced cortisol responsivity to psychological stress in women using oral contraceptive medication. *Psychoneuroendocrinology, 20*(5), 509-514.

Kirschbaum, C., Pirke, K. M., & Hellhammer, D. H. (1993). The 'Trier Social Stress Test' – a tool for investigating psychobiological stress response in a laboratory setting. *Neuropsychobiology, 28*, 76-81.

Kirschbaum, C., Tietze, A., Skoluda, N., & Dettenborn, L. (2008). Hair as a retrospective calendar of cortisol production—increased cortisol incorporation into hair in the third trimester of pregnancy. *Psychoneuroendocrinology*.

Knudsen, A. K., Henderson, M., Harvey, S. B., & Chalder, T. (2011). Long-term sickness absence among patients with chronic fatigue syndrome. *The British Journal of Psychiatry, 199*, 430-431.

Kovacs, M. (1992). *Children's Depression Inventory (CDI) manual*: New York: Multi-Health Systems.

Kovacs, M., & Beck, A. (1977). An empirical-clinical approach toward a definition of childhood depression. In J. S. A. Raskin (Ed.), *Depression in childhood: Diagnosis. treatment and conceptual models* (pp. 1-26): Washington, DC: Department of Health, Education and Welfare.

Krantz, D. S., & McCeney, M. K. (2002). Effects of psychological and social factors on organic disease: A critical assessment of research on coronary heart disease. *Annual review of psychology, 53*, 341-369.

Krilov, L. R., Fisher, M., Friedman, S. B., Reitman, D., & Mandel, F. S. (1998). Course and Outcome of Chronic Fatigue in Children and Adolescents. *Pediatrics, 102*(2), 360-366.

Ladouceur, R., Dugas, M. J., Freeston, M. H., Leger, E., Gagnon, F., & Thibodeau, N. (2000). Efficacy of a cognitive-behavioral treatment for generalized anxiety disorder: Evaluation in a controlled clinical trial. *Journal of Consulting and Clinical Psychology, 68*(6), 957-964.

Lang, P. J., Levin, D. N., Miller, G. A., & Kozac, M. J. (1983). Fear behaviour, fear imagery and the psychophysiology of emotion: The problem of affective response integration. *Journal of abnormal psychology, 92*, 276-306.

Lauer, M. S. (2001). Exercise Electrocardiogram Testing and Prognosis: Novel Markers and Predictive Instruments. *Cardiology Clinician, 19*, 401-414.

Lawrie, S. M., Manders, D. N., Geddes, J. R., & Pelosi, A. J. (1997). A population-based incidence study of chronic fatigue. *Psychological Medicine, 27*(2), 343-353.

Li, L., & Chen, J. (2006). Emotion recognition using physiological signals. *Lecture Notes in Computer Science, 4282*, 437-446.

Lievesley, K., Rimes, K. A., & Chalder, T. (2014). A review of the predisposing, precipitating and perpetuating factors in Chronic Fatigue Syndrome in children and adolescents. *Clinical Psychology Review, 34*, 233-248.

Lipworth, B. J. (1999). Systemic Adverse Effects of Inhaled Corticosteroid Therapy: A Systematic Review and Meta-analysis. *Archives of International Medicine, 159*(9), 941-955.

Little, R. J. A. (1998). A test of missing completely at random for multivariate data with missing values. *Journal of the American Statistical Association, 83*, 1198-1202.

Lloyd, A. R., Hickie, I., Boughton, C. R., Spencer, O., & Wakefield, D. (1990). Prevalence of chronic fatigue syndrome in an Australian population. *Medical Journal of Australia, 153*, 522-528.

Lloyd, S., Chalder, T., & Rimes, K. A. (2012). Family-focused cognitive behaviour therapy versus psycho-education for adolescents with chronic fatigue syndrome: Long-term follow-up of an RCT. *Behaviour Research and Therapy, 50*(11), 719-725.

Lloyd, S., Chalder, T., Sallis, H. M., & Rimes, K. A. (2012b). Telephone-based guided self-help for adolescents with chronic fatigue syndrome: A non-randomised cohort study. *Behaviour Research and Therapy, 50*(5), 304-312.

Luthra, A., & Wessely, S. (2004). Unloading the trunk: neurasthenia, CFS and race. *Social Science and Medicine, 58*(11), 2363-2369.

Lyall, M., Peakman, M., & Wessely, S. (2003). A systematic review and critical evaluation of the immunology of chronic fatigue syndrome. *Journal of Psychosomatic Research, 55*(2), 79-90.

Lyubomirsky, S., Caldwell, N. D., & Nolen-Hoeksema, S. (1998). Effects of ruminative and distracting responses to depressed mood on retrieval of autobiographical memories. *Journal of Personality, 75*, 166-177.

Lyubomirsky, S., & Nolen-Hoeksema, S. (1993). Self-perpetuating properties of dysphoric rumination. *Journal of Personality and social psychology, 65*, 339-349.

Lyubomirsky, S., & Tkach, C. (2004). The consequences of dysphoric rumination. In C. P. A. Wells (Ed.), *Rumination: Nature, theory, and treatment of negative thinking in depression* (pp. 21-41): Chichester, England: John Wiley & Sons.

MacHale, S. M., Cavanagh, J. T. O., Bennie, J., Carroll, S., Goodwin, G. M., & Lawrie, S. M. (1998). Diurnal variation of adrenocortical activity in chronic fatigue syndrome. *Neuropsychobiology, 38*(4), 213-217.

Malik, A. (2011). Heart Rate Variability. *Anaesthesia update, 14*(1), 6-7.

Malik, M. (1996). Heart Rate Variability. *Annals of Noninvasive Electrocardiology, 1*, 151-181.

Malliani, A., Lombardi, F., & Pagani, M. (1994). Power spectrum analysis of heart rate variability: a tool to explore neural regulatory mechanisms. *British Heart Journal, 71*, 1-2.

Malmo, R. B., Shagass, C., & Davis, F. H. (1950). Symptom specificity and bodily reactions during psychiatric interview. *Psychosomatic Medicine, 12*, 362-376.

Mansell, W., Harvey, A., Watkins, E., & Shafran, R. (2009). Conceptual Foundations of the Transdiagnostic Approach to CBT. *Journal of Cognitive Psychotherapy, 23*(1), 6-19.

Marshall, G. S., Gesser, R. M., Yamanishi, K., & Starr, S. E. (1991). Chronic fatigue in children: clinical features, epstein-barr virus and human herpesvirus 6 serology and long term follow-up. *Pediatric Infectious Diseases Journal, 10*(4), 287-290.

May, M., Emond, A., & Crawley, E. (2009). Phenotypes of Chronic Fatigue Syndrome in Children and Young People. *Archives of Disease in Childhood, 95*, 245-249.

McCrae, R. R., & Costa, P. T., Jr. (1986). Personality, coping, and coping effectiveness in an adult sample. *Journal of Personality, 54*, 385-405.

Metzger, F. A., & Denney, D. R. (2002). Perception of cognitive performance in patients with chronic fatigue syndrome. *Annals of Behavioural Medicine, 24*, 106-112.

Miller-Day, M., & Marks, J. D. (2006). Perceptions of parental communication orientation, perfectionism, and disordered eating behaviors of sons and daughters. *Health Communication, 19*(2), 153-163.

Miller, D. B., & O'Callaghan, J. P. (2002). Neuroendocrine aspects of the response to stress. *Metabolism, 51*(6 Part B), 5-10.

Missen, A., Hollingworth, W., Eaton, N., & Crawley, E. (2012). The financial and psychological impacts on mothers of children with chronic fatigue syndrome (CFS/ME). *Child Care Health Development, 38*(4), 505-512.

Moore, K. L., & Agur, A. M. (2007). *Essential Clinical Anatomy: Third Edition* (Vol. 42). Baltimore: Lippincott Williams & Wilkins.

Morrow, J., & Nolen-Hoeksema, S. (1990). Effects of responses to depression on the remediation of depressive affect. *Journal of Personality and social psychology, 58*, 519-527.

Moss-Morris, R., & Chalder, T. (2003). Illness perceptions and levels of disability in patients with chronic fatigue syndrome and rheumatoid arthritis. *Journal of Psychosomatic Research, 55*(4), 305-308.

Moss-Morris, R., Sharon, C., Tobin, R., & Baldi, J. C. (2005). A randomised controlled graded exercise trial for chronic fatigue syndrome: outcomes and mechanisms of change. *Journal of Psychology, 10*, 245-259.

Moss-Morris, R., Skerret, T., Chalder, T., & Balwin, M. (2004). *The role of cognitive behavioural responses to symptoms in chronic fatigue syndrome and multiple sclerosis*. Paper presented at the Eighth International Congress of Behavioural Medicine, Mainz, Germany.

Moss-Morris, R., Spence, M. J., & Hou, R. (2011). The pathway from glandular fever to chronic fatigue syndrome: can the cognitive behavioural model provide the map? *Psychological Medicine, 41*, 1099-1107.

Moss-Morris, R., Weinman, J., Petrie, K. J., Horne, R., Cameron, L. D., & Buick, D. (2002). The revised illness perception questionnaire (IPQ-R). *Psychology and Health, 17*(1), 1-16.

Mundt, J. C., Marks, I. M., Shear, M. K., & Greist, J. H. (2002). The Work and Social Adjustment Scale: a simple measure of impairment in functioning. *British Journal of Psychiatry, 180*, 461-464.

Nederhof, A. J. (2006). Methods of coping with social desirability bias: A review. *European Journal of Social Psychology, 15*, 263-280.

Newcomer, K. L., Krug, H. E., & Mahowald, M. L. (1993). Validity and reliability of the timed-stands test for patients with rheumatoid arthritis and other chronic diseases. *Journal of Rheumatology, 20*(1), 21-27.

Newton, T. L., & Contrada, R. J. (1992). Repressive coping and verbal-autonomic response dissociation: the influence of social context. *Journal of Personality and social psychology, 62*(1), 159-167.

NICE. (2007). *Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (or Encephalopathy); Diagnosis and Management*: CG53. London: National Institute for Health and Clinical Excellence (NICE).

Nicolson, N. A. (2008). Measurement of cortisol.

Nijhof, S. L., Bleijenberg, G., Uiterwaal, C. S. P. M., Kimpen, J. L. L., & van de Putte, E. M. (2012). Effectiveness of internet-based cognitive behavioural treatment for adolescents with chronic fatigue syndrome (FITNET): a randomised controlled trial. *Lancet, 29*.

Nijhof, S. L., Maijer, K., Bleijenberg, G., Uiterwaal, C. S. P. M., Kimpen, J. L. L., & van de Putte, E. M. (2011). Adolescent Chronic Fatigue Syndrome: Prevalence, Incidence and Morbidity. *Pediatrics, 127*, 1169-1175.

Nijs, J., Paul, L., & Wallman, K. (2008). Chronic fatigue syndrome: an approach combining self-management with graded exercise to avoid exacerbations. *Journal of Rehabilitation Medicine, 40*(4), 241-247.

Nisenbaum, R., Reyes, M., Unger, E. R., & Reeves, W. C. (2004). Factor analysis of symptoms among subjects with unexplained chronic fatigue: what can we learn about chronic fatigue syndrome? . *Journal of Psychosomatic Research, 56*, 171-178.

Nolen-Hoeksema, S. (1991). Responses to depression and their effects on the duration of depressive episodes. *Journal of abnormal psychology, 100*, 569-582.

Nolen-Hoeksema, S. (1998). The other end of the continuum: The costs of rumination. *Psychological Inquiry, 9*, 216-219.

Nolen-Hoeksema, S., & Davis, C. G. (1999). "Thanks for sharing that": Ruminators and their social support networks. *Journal of Personality and social psychology, 77*, 801-814.

Nolen-Hoeksema, S., & Morrow, J. (1993). Effects of rumination and distraction on naturally occuring depressed mood. *Cognition and Emotion, 7*, 561-570.

Pacht, A. R. (1984). Reflections on perfection. *American Psychologist, 39*, 386-390.

Padget, D. A., & Glaser, R. (2003). How stress influences the immune system. *Trends in Immunology, 24*(8), 444-448.

Papadopolous, A. S., & Cleare, A. J. (2012). Hypothalamic-pituitary-adrenal axis dysfunction in chronic fatigue syndrome. *Endocrinology, Nature Reviews, 8*(1), 22-32.

Parker, G. (1979). Reported Parental Characteristics in Relation to Trait Depression and Anxiety Levels in a Non-Clinical Group. *Australian and New Zealand Journal of Psychiatry, 13*(3), 260-264.

Parker, G. (1983). *Parental overprotection: A risk factor in psychosocial development*. New York: Grune & Stratton.

Parker, G. (1989). The parental bonding instrument: Psychometric properties reviewed. *Psychiatry Development, 4*, 317-335.

Parker, G., Tupling, H., & Brown, L. B. (1979). A parental bonding instrument. *British Journal of Medical Psychology, 52*, 1-10.

Patel, M. X., Smith, D. G., Chalder, T., & Wessely, S. (2003). Chronic Fatigue Syndrome in children: a cross sectional survey. *Archives of Disease in Childhood, 88*, 894-898.

Pelcovitz, D., Septimus, A., Friedman, S. B., Krilov, L. R., Mandel, F., & Kaplan, S. (1995). Psychosocial Correlates of Chronic Fatigue Syndrome in adolescent girls. *Developmental and Behavioural Pediatrics, 16*(5), 333-338.

Pennebaker, J. W. (1982). *The Psychology of Physical Symptoms*: Springer-Verlag, New York.

Pennebaker, J. W., & Skelton, J. A. (1978). Psychological Parameters of Physical Symptoms. *Personality and Social Psychology Bulletin, 4*, 524-530.

Pereda, N., Guilera, G., Forns, M., & Gómez-Benito, J. (2009). The international epidemiology of child sexual abuse: a continuation of Finkelhor (1994). *Child Abuse & Neglect, 33*, 331-342.

Petrie, K., Moss-Morris, R., & Weinman, J. (1995). The impact of catastrophic beliefs on functioning in chronic fatigue syndrome. *Journal of Psychosomatic Research, 39*, 31-37.

Petrov, D., Marchalik, D., Sosin, M., & Bal, A. (2011). Factors affecting duration of Chronic Fatigue Syndrome in pediatric patients. *Indian Journal of Pediatrics, 79*(1), 52-55.

Pickles, A. (2005). Missing data, problems and solutions. In K. Kempf-Leonard (Ed.), *Encyclopedia of social measurement* (pp. 689-694). Amsterdam: Elsevier.

Pinquart, M. (2012). Self-esteem of children and adolescents with chronic illness: a meta-analysis. *Child: care, health and development, 39*(2), 153-161.

Pruessner, J. C., Kirschbaum, C., Meinlschmid, G., & Hellhammer, D. H. (2003). Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. *Psychoneuroendocrinology, 28*(7), 916-931.

Rangel, L., Garralda, E., Hall, A., & Woodham, S. (2003). Psychiatric adjustment in Chronic Fatigue Syndrome of childhood and in juvenile idiopathic arthritis. *Psychological Medicine, 33*, 289-297.

Rangel, L., Garralda, E., Jeffs, J., & Rose, G. (2005). Family health and characteristics in Chronic Fatigue Syndrome, Juvenile Rheumatoid Arthritis, and Emotional Disorders of Childhood. *Journal of American Academy of Child and Adolescent Psychiatry, 44*(2), 150-158.

Rangel, L., Garralda, E., Levin, M., & Roberts, H. (2000a). Personality in adolescents with Chronic Fatigue Syndrome. *European Child and Adolescent Psychiatry, 9*, 129-134.

Rangel, L., Garralda, E., Levin, M., & Roberts, H. (2000b). The course of severe Chronic Fatigue Syndrome in childhood. *Journal for the Royal Society of Medicine, 93*, 129-134.

Rangel, L., Rapp, S., Levin, M., & Garralda, M. E. (1999). Chronic fatigue syndrome: Updates on paediatric and psychological management. *Current Paediatrics, 9*, 188-193.

Rapee, R. M. (1997). Potential role of childrearing practices in the development of anxiety and depression. *Clinical Psychology Review, 17*(1), 47-67.

Rapee, R. M., & Lim, L. (1992). Discrepancy between self and observer ratings of performance in social phobics. *Journal of abnormal psychology, 101*, 727-731.

Ray, C., Weir, W., Stewart, D., Miller, P., & Hyde, G. (1993). Ways of coping with chronic fatigue syndrome: Development of an illness management questionnaire. *Social Science & Medicine, 37*, 385-391.

Reichlin, S. (1998). Neuroendocrinology. In J. D. Wilson (Ed.), *Textbook of Endocrinology (9th edn)* (pp. 165-248): W B Saunders.

Reid, S., Wessely, S., Crayford, T., & Hotopf, M. (2001). *Medically unexplained symptoms in frequent attenders of secondary health care: retrospective cohort study* (Vol. 322).

Richards, J., Chaplin, R., Starkey, C., & Turk, J. (2006). Illness Beliefs in Chronic Fatigue Syndrome: A study involving affected adolescents and their parents. *Child and Adolescent Mental Health, 11*(4), 198-203.

Richards, J., Turk, J., & White, S. (2005). Chidlren and adolescents with Chronic Fatigue Syndrome in non specialist settings: Beliefs, functional impairment and psychiatric disturbance. *European Child and Adolescent Psychiatry, 14*, 310-318.

Rimes, K. A., & Chalder, T. (2010). The beliefs about emotions scale: Validity, reliability and sensitivity to change. *Journal of Psychosomatic Research, 68*(3), 285-292.

Rimes, K. A., Goodman, R., Hotopf, M., Wessely, S., Meltzer, H., & Chalder, T. (2007). Incidence, Prognosis, and Risk Factors for Fatigue and Chronic Fatigue Syndrome in Adolescents: A prospective Community Study. *Pediatrics, 119*(3), 603-609.

Rimes, K. A., Papadopolous, A. S., Cleare, A. J., & Chalder, T. (unpublished-a). Cortisol output and awakening response in adolescents with chronic fatigue syndrome before and after treatment.

Rimes, K. A., Papadopolous, A. S., Cleare, A. J., & Chalder, T. (unpublished-b). Salivary cortisol in adolescents with chronic fatigue syndrome: comparison with

healthy controls and relationships with measures of perfectionism and prosocial behaviour.

Robbins, J. M., & Kirmayer, L. J. (1991). Attributions of common somatic symptoms. *Psychological Medicine, 21*(4), 1029-1045.

Roberts, A. D. L., Papadopoulos, A. S., Wessely, S., Chalder, T., & Cleare, A. J. (2008). Salivary cortisol output before and after cognitive behavioural therapy for chronic fatigue syndrome. *Journal of Affective Disorders, 115*(1-2), 280-286.

Roberts, A. D. L., Wessely, S., Chalder, T., Papadopoulos, A., & Cleare, A. J. (2004). Salivary cortisol response to awakening in chronic fatigue syndrome. *British Journal of Psychiatry, 184*, 136-141.

Rodgers, B. (1990). Behaviour and personality in childhood as predictors of adult psychiatric disorder. *Journal of Child Psychology and Psychiatry, 31*, 393-414.

Roth, W. T., Ehlers, A. T., Taylor, C. B., Margraf, J., & Agras, W. S. (1990). Skin conductance habituation in panic disorder patients. *Biological Psychiatry, 27*(11), 1231-1243.

Rowe, K. S., & Rowe, K. J. (2002). Symptom patterns of children and adolescents with chronic fatigue syndrome. In T. H. O. In N.N. Singh, & A.N. Singh (Ed.), *International Perspectives on Child and Adolescent Mental Health* (Vol. 2, pp. 395-421): Elsevier Science Ltd.: Oxford.

Rubin, D. B. (1976). Inference with missing data. *Biometrika, 63*, 581-592.

Rutter, M., Tizard, J., & Whitmore, K. (1970). *Education, health and behaviour*: London: Longmans.

Salkovskis, P. M., & Warwick, H. M. C. (1986). Morbid preoccupations, health anxiety and reassurance: A cognitive-behavioural approach to hypochondriasis. *Behaviour Research and Therapy, 24*, 597-602.

Sankey, A., Hill, C. M., Brown, J., Quinn, L., & Fletcher, A. (2006). A follow-up study of Chronic Fatigue Syndrome in Children and Adolescents: Symptom Persistence and School Absenteeism. *Clinical Child Psychology and Psychiatry, 11*(1), 126-138.

Schniering, C. A., Hudson, J. L., & Rapee, R. M. (2000). Issues in the diagnosis and assessment of anxiety disorders in children and adolescents. *Clinical Psychology Review, 20*(4), 453-478.

Segal, T. Y., Hindmarsh, P. C., & Viner, R. M. (2005). Disturbed Adrenal Function in Adolescents with Chronic Fatigue Syndrome. *Journal of Pediatric Endocrinology & Metabolism, 18*, 295-301.

Shafran, R., Cooper, Z., & Fairburn, C. G. (2002). Clinical perfectionism: a cognitive-behavioural analysis. *Behaviour and Research Therapy, 40*(7), 773-791.

Sharpe, M. C., Archard, L. C., Banatvala, J. E., Borysiewicz, L. K., Clare, A. W., David, A., . . . White, P. D. (1991). A report - chronic fatigue syndrome: guidelines for research. *Journal for the Royal Society of Medicine, 84*(February 1991), 118-121.

Sharpe, M. C., Hawton, K., Seagroatt, V., & Pasovl, G. (1992). Follow up of patients presenting with fatigue to an infectious diseases clinic. *British Medical Journal, 305*(6846), 147-152.

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorium, P., Janvas, J., Weiller, E., . . . Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry, 59 Supplement*(20), 22-33.

Sheehan, D. V., Sheehan, K. H., Shytle, R. D., Janvas, J., Bannon, Y., Rogers, J. E., . . . Wilkinson, B. (2010). Reliability and validity of the Mini International

Neuropsychiatric Interview for Children and Adolescents (MINIKID). *Journal of Clinical Psychiatry, 71*(3), 313-326.

Skerrett, T. N., & Moss-Morris, R. (2006). Fatigue and social impairment in multiple-sclerosis: the role of patients' cognitive and behavioural responses to their symptoms. *Journal of Psychosomatic Research, 61*, 587-593.

Smith, B. (2013). Depression and motivation. *Phenomenology and the cognitive sciences, 12*(4), 615-635.

Smith, M. S., Buchwald, D. S., Bogart, A., Goldberg, J., Smith, W. R., & Afari, N. (2010). Adolescent Offspring of Mothers with Chronic Fatigue Syndrome. *Journal of Adolescent Health, 46*, 284-291.

Smith, M. S., Martin-Herz, S. P., Womack, W. M., & Marsigan, J. L. (2003). Comparative study of anxiety, depression, omatization, functional disability, and illness attribution in adolescents with chronic fatigue or migraine. *Pediatrics, 111*, 376-381.

Smith, M. S., Mitchell, J., Corey, L., Gold, D., McCauley, E. A., Glover, D., & Tenover, F. C. (1991). Chronic Fatigue in Adolescents. *Pediatrics, 88*(2), 195-202.

Solomon, L., Nisenbaum, R., Reyes, M., Papanicolaou, D., & Reeves, W. (2003). Functional status of persons with chronic fatigue syndrome in the Wichita, Kansas, population. *Health and Quality of Life Outcomes, 1*(1), 48.

Sommerfeldt, L., Portilla, H., Jacobsen, L., Gjerstad, J., & Wyller, V. B. (2011). Polymorphisms of adrenergic cardiovascular control genes are associated with adolescent chronic fatigue syndrome. *Acta Pediatrica: Nurturing the Child, 100*, 293-298.

Spence, S. H. (1998). A measure of anxiety symptoms among children. *Behaviour Research and Therapy, 36*, 545-566.

Spence, S. H., Najman, J. M., Bor, W., O'Callaghan, M. J., & Williams, G. M. (2002). Maternal anxiety and depression, poverty and marital relationship factors during early childhood as predictors of anxiety and depressive symptoms in adolescence. *The journal of child psychology and psychiatry, 43*(4), 457-469.

Spence, V., & Stewart, J. (2004). Standing up for ME. *Biologist, 51*(2), 65-70.

Spielberger, C. (1973). *STAIC preliminary manual*. Palo Alto, CA: Consulting Psychologists Press.

Stahl, D., Rimes, K., & Chalder, T. (2014). Mechanisms of change underlying the efficacy of cognitive behaviour therapy for chronic fatigue syndrome in a specialist clinic: a mediation analysis. *Psychological Medicine, 44*(6), 1331-1344.

Steele, L., Dobbins, J. G., Fukuda, K., Reyes, M., Randall, B., Koppelman, M., & Reeves, W. C. (1998). The epidemiology of chronic fatigue in San Francisco. *American Journal of Medicine, 105*(supplement), 83S-90S.

Stewart, A. L., Hays, R. D., & Ware Jr., J. E. (1998a). The MOS Short-form general health survey: Reliability and validity in a patient population. *Medical care, 26*, 724-735.

Stewart, J. M. (2000). Autonomic Nervous System Dysfunction in adolescents with postural orthostatic tachycardia syndrome and chronic fatigue syndrome is characterised by attenuated vagal baroreflex and potential sympathetic vasomotion. *Pediatric Research, 48*(2), 218-226.

Stewart, J. M., Gewitz, M. H., Weldon, A., Arlievsky, N., Li, K., & Munoz, J. (1999). Orthostatic intolerance in adolescent Chronic Fatigue Syndrome. *Pediatrics, 103*(1), 116-121.

Stewart, J. M., Weldon, A., Arlievsky, N., Li, K., & Munoz, J. (1998b). Neurally mediated hypotension and autonomic dysfunction measured by heart rate variability during head-up tilt testing in children with chronic fatigue syndrome. *Clinical Autonomic Research, 8*, 221-230.

Stoeber, J., & Childs, J. H. (2014). Perfectionism. In R. J. R. Levesque (Ed.), *Encyclopedia of adolescence*. New York: Springer.

Stratton, P., Bland, J., Janes, E., & Lask, J. (2010). Developing a practicable outcome measure for systemic family therapy: The SCORE. *Journal of Family Therapy, 32*, 232-258.

Stulemeijer, M., de Jong, W. A. M. L., Fiselier, T. J. W., Hoogveld, S. W. B., & Bleijenberg, G. (*2005*). Cognitive behaviour therapy for adolescents with Chronic Fatigue Syndrome: randomised controlled trial. *British Medical Journal, 330*(14), 1-5.

Stumpf, H., & Parker, W. D. (2000). A hierarchical structural analysis of perfectionism and its relation to other personality characteristics. *Personality and Individual Differences, 28*, 837-852.

Sulheim, D., Hurum, H., Helland, I. B., Thaulow, E., & Wyller, V. B. (2012). Adolescent chronic fatigue syndrome; a follow-up study displays concurrent improvement of circulatory abnormalities and clinical symptoms. *BioPsychoSocial Medicine, 6*, 10.

Surarwy, C., Hackmann, A., Hawton, K., & Sharpe, M. (1995). Chronic fatigue Syndrome: a cognitive approach. *Behaviour Research Therapy, 33*, 535-544.

Sweis, B. M. (2012). A basic HPA Axis function. (http://en.wikipedia.org/wiki/Hypothalamic%E2%80%93pituitary%E2%80%93adrenal_axis).

Teasdale, J. D., & Dent, J. (1987). Cognitive vulnerability to depression: An investigation of two hypotheses. *British Journal of Clinical Psychology, 26*(2), 113-126.

ter Wolbeek, M., van Doornen, L. J. P., Kavelaars, A., Tersteeg-Kamperman, M. D. J., & Heijnen, C. J. (2011). Fatigue, depressive symptoms and anxiety from adolescence up to young adulthood: A longitudinal study. *Brain, Behaviour and Immunity, 25*, 1249-1255.

ter Wolbeek, M., van Doornen, L. J. P., Kavelaars, A., van de Putte, E. M., Schedlowski, M., & Heijnen, C. J. (2007). Longitudinal analysis of pro- and anti-inflammatory cytokine production in severely fatigued adolescents. *Brain, Behaviour and Immunity, 21*(8), 1063-1074.

Tomas, C., Newton, J., & Watson, S. (2013). A Review of Hypothalamic-Pituitary-Adrenal Axis Function in Chronic Fatigue Syndrome,. *SRN Neuroscience, 2013*, 8 pages.

Trivette, C. M., Dunst, C. J., Deal, A. G., Hamer, A. W., & Propst, S. (1990). Assessing family strengths and family functioning style. *Topics in Early Childhood Special Education, 10*(1), 16-35.

Tsuji, H., Larson, M. G., Venditti Jr, F. J., Manders, E. S., Evans, J. C., Feldman, C. L., & Levy, D. (1996). Impact of reduced heart rate variability on risk for cardiac events. The Framingham Heart Study. *Circulation, 94*, 2850-2855.

Tulisalo, U. K., & Aro, H. M. (2000). Paternal remarriage as modifier of proneness to depression in young adulthood. *Journal of Affective Disorders, 57*, 179-184.

Tyrer, P., & Alexander, J. (1979). Classification of personality disorder. *British Journal of Psychiatry, 135*, 238-242.

Uttl, B., & Pilkenton-Taylor, C. (2001). Letter cancellation performance across the adult life span. *Clinical Neuropsychology, 15*, 521-530.

van de Putte, E. M., Bocker, K. B., Buitelaar, J., Leon Kenemans, J., Engelbert, R. H. H., Kuis, W., . . . Uiterwaal, C. S. P. M. (2008). Deficits of Interference Control in Adolescents with Chronic Fatigue Syndrome. *Archives of Pediatric and Adolescent Medicine, 162*(12), 1106-1107.

van de Putte, E. M., Engelbert, R. H. H., Kuis, W., Sinnema, G., Kimpen, J. L. L., & Uiterwaal, C. S. P. M. (2005). Chronic fatigue syndrome and health control in adolescents and parents. *Archives of Disease in Childhood, 90*, 1020-1024.

van de Putte, E. M., van Doornen, L. J. P., Engelbert, R. H. H., Kuis, W., Kimpen, J. L. L. , & Uiterwaal, C. S. P. M. (2006). Mirrored symptoms in mother and child with Chronic Fatigue Syndrome. *Pediatrics, 117*, 2074-2079.

van Geelan, S. M., Bakker, R. J., Kuis, W., & van de Putte, E. M. (2010). Adolescent Chronic Fatigue Syndrome. *Archives of Pediatric and Adolescent Medicine, 164*(9), 810-814.

van Middendorp, H., Geenen, R., Kuis, W., Heijnen, C. J., & Sinnema, G. (2001). Psychological adjustment of adolescent girls with chronic fatigue syndrome. *Pediatrics, 107*(3), E35.

Varni, J., Seid, M., & Rode, C. (1999). The Peds QL: Measurement model for the Pediatric Quality of Life Inventory. *Medical care, 37*, 126-139.

Varni, J. W., Seid, M., & Kurtin, P. S. (2001). The PedsQL 4.0TM: Reliability and validity of the Pediatric Quality of Life InventoryTM Version 4.0 Generic Core Scales in healthy and patient populations. *Medical care, 39*, 800-812.

Vaughn, C. E., & Leff, J. (1976). The measurement of expressed emotion in the families of psychiatric patients. *British Journal of Social and Clinical Psychology, 15*, 157-165.

Venables, P. H., & Christie, M. J. (1973). Mechanisms, instrumentation, recording techniques and quantification of responses *In Prokasy & Raskin* (pp. 1-124).

Venables, P. H., & Christie, M. J. (1980). Electrodermal activity. In I. M. P. H. Venables (Ed.), *Techniques in psychophysiology* (pp. 3-67). Chichester, UK: John Wiley & Sons.

Vercoulen, J. H., Swanink, C. M., Galama, J. M., Fennis, J. F., Jongen, P. J., Hommes, O. R., . . . Bleijenberg, G. (1998). The persistence of fatigue in chronic fatigue syndrome and multiple sclerosis: development of a model. *Journal of Psychosomatic Research, 45*, 507-517.

Vercoulen, J. H. M. M., Swanink, C. M. A., Fennis, J. F. M., Galama, J. M. D., van der Meer, J. W. M., & Bleijenberg, G. (1994). Dimensional assessment of chronic fatigue syndrome. *Journal of Psychosomatic Research, 38*(5), 383-392.

Vereker, M. I. (1992). Chronic fatigue syndrome: a joint paediatric approach. *Archives of Disease in Childhood, 67*, 550-555.

Vervoort, T., Crombez, G., Buysse, A., Goubert, L., De Backer, T., & Ickes, W. (2007). Brief Report: The accuracy of parents for thoughts and feelings of their adolescent suffering from Chronic Fatigue: A preliminary study of empathy. *Journal of Pediatric Psychology, 32*(4), 494-499.

Vieth, A. Z., & Trull, T. J. (1999). Family patterns of perfectionism: An examination of college students and their parents. *Journal of Personality Assessment, 72*, 49-67.

Viner, R., & Christie, D. (2005). Fatigue and somatic symptoms. *British Medical Journal, 330*, 1012-1015.

Viner, R., & Hotopf, M. (2004). Childhood predictors of self-reported Chronic Fatigue Syndrome / Myalgic Encephalomyelitis in adults: national birth cohort study. *British Medical Journal, 329*, 941-945.

Vining, R. F., & McGinley, R. A. (1986). Hormones in Saliva. *Critical Reviews in Clinical Laboratory Sciences, 23*(2), 95.

Vining, R. F., & McGinley, R. A. (1987). The measurement of hormones in saliva: possibilities and pitfalls. *Journal of Steroid Biochemistry, 27*(1-3), 81-94.

Vining, R. F., McGinley, R. A., Maksvytis, J. J., & Ho, K. Y. (1983). Salivary cortisol: A better measure of adrenal cortical function than serum cortisol. *Annals of Clinical Biochemistry, 20*, 329-335.

Walford, G. A., Nelson, W., & McCluskey, D. R. (1993). Fatigue, depression and social adjustment in chronic fatigue syndrome. *Archives of Disease in Childhood, 68*, 384-388.

Wallston, K. A., Wallston, B. S., & DeVellis, R. (1978). Development of the Multidimensional Health Locus of Control (MHLC) Scales. *Health Education Monographs, 6*, 160-170.

Walschburger, P. (1976). *Zur Beschreibung von Aktivierungsprozessen: Eine Methodenstudie zur psychophysiologischen Diagnostik*. Unpublished Doctoral Dissertation.

Ware, J. E., Sherbourne, C. D., & Davies, A. R. (1992). Developing and testing the MOS 20-Item Short-Form Health Survey: A general population application In A. L. S. J. E. Ware (Ed.), *Measuring functioning and well-being: The Medical Outcomes Study approach* (pp. 277-290). Durham, NC: Duke University Press.

Wechsler, D. (1999). *Wechsler Abbreviated Scale of Intelligence*. San Antonio, TX: Psychological Corporation

Weinman, J., Petrie, K. J., Moss-Morris, R., & Horne, R. (1996). The Illness Perception Questionnaire: a new method for assessing the cognitive representation of illness. *Psychology and Health, 11*, 431-444.

Wenzlaff, R. M., & Wegner, D. M. (2000). Thought suppression. *Annual review of psychology, 51*, 59-91.

Wessely, S., Chalder, T., Hirsch, S., & Wallace, P. (1996). Psychological Symptoms, Somatic Symptoms, and Psychiatric Disorder in Chronic Fatigue and Chronic Fatigue Syndrome: A Prospective Study in the Primary Care Setting. *American Journal of Psychiatry, 153*, 1050-1059.

Wessely, S., David, A. S., Butler, D. S., & Chalder, T. (1989). Management of chronic (post-viral) fatigue syndrome. *Journal of the Royal College of General Practitioners, 39*, 26-29.

Westbury, H. R., & Neumann, D. L. (2008). Empathy-related responses to moving film stimuli depicting human and non-human animal targets in negative circumstances. *Biological Psychology, 78*, 66-74.

Westen, D., Shedler, J., Durrett, C., Glass, S., & Martens, A. (2003). Personality diagnoses in adolescence: DSM-IV Axis II diagnoses and an empirically derived alternative. *American Journal of Psychiatry, 160*, 952-966.

White, C., & Schweitzer, R. (2000). The role of personality in the development and perpetuation of chronic fatigue syndrome. *Journal of Psychosomatic Research, 48*, 515-524.

Wiborg, J. F., Knoop, H., Prins, J. B., & Bleijenberg, G. (2011). Does a decrease in avoidance behaviour and focusing on fatigue mediate the effect of cognitive behaviour therapy for chronic fatigue syndrome? *Journal of Psychosomatic Research, 70*, 306-310.

Wilson, A., Hickie, I., Hadzi-Pavlovic, D., Wakefield, D., Parker, G., Strauss, S. E., . . . Lloyd, A. (2001). What is Chronic Fatigue Syndrome? Heterogeneity within an international multicentre study. *Australian and New Zealand Journal of Psychology, 35*, 520-527.

Wood, B., & Wessely, S. (1999). Personality and social attitudes in chronic fatigue syndrome. *Journal of Psychosomatic Research, 47*, 385-397.

Wood, J. J., Placentini, J. C., Southam-Gerow, M., Chu, B. C., & Sigman, M. (2006). Family cognitive behavioural therapy for child anxiety disorders. *Journal of the American Academy of Child & Adolescent Psychiatry, 45*(3), 314-321.

Wyller, V. B., Barbieri, R., & Saul, J. P. (2011). Blood pressure variability and closed-loop baroreflex assessment in adolescent chronic fatigue syndrome during supine rest and orthostatic stress. *European Journal of Applied Physiology, 111*, 497-507.

Wyller, V. B., Barbieri, R., Thaulow, E., & Saul, J. P. (2008). Enhanced vagal withdrawal during mild orthostatic stress in adolescents with chronic fatigue. *Annals of Noninvasive Electrocardiology, 13*(1), 67-73.

Wyller, V. B., Due, R., Saul, J. P., Amlie, J. P., & Thaulow, E. (2007a). Usefulness of an abnormal cardiovascular response during low-grade head-up tilt-test for discriminating adolescetns with chronic fatigue from healthy controls. *The American Journal of Cardiology, 99*(7), 997-1001.

Wyller, V. B., Eriksen H. R., & K., M. (2009). Can sustained arousal explain the Chronic Fatigue Syndrome? *Behaviour and Brain Function, 5*, 10.

Wyller, V. B., Evang, J. A., Godang, K., Solhjell, K. K., & Bollerslev, J. (2010). Hormonal alterations in adolescent chronic fatigue syndrome. *Acta Paediatrica: Nurturing the Child, 99*(5), 770-773.

Wyller, V. B., Saul, J. P., Amlie, J. P., & Thaulow, E. (2007b). Sympathetic predominance of cardiovascular regulation during mild orthostatic stress in adolescents with chronic fatigue. *Clinical Physiology and Functional Imaging, 27*(4), 231-238.

Wyller, V. B., Saul, J. P., Walloe, L., & Thaulow, E. (2007c). Sympathetic cardiovascular control during orthostatic stress and isometric exercise in adolescent chronic fatigue syndrome. *European Journal of Applied Physiology, 102*(6), 623-632.

Young, J. E. (1990). *Cognitive therapy for personality disorders: A schema focused approach*. Sarasota, FL: Professional Resource Exchange, Inc.

Zigmond, A. S., & Snaith, R. P. (1983). The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica, 67*(6), 361-370.

Appendices

Appendix 1: Ethical amendments list

Ethical approval was sought and granted by the following bodies, the Local Research Ethics Committee (LREC; ref. 08/H0807/107), for Institute of Psychiatry (September 2009, R&D), Guys & St. Thomas' Hospitals (March 2011), Great Ormond Street Hospital (October 2010). Seven ethical amendments were submitted and approved during the study and are listed below:

- Amendment 1: The use of the Mini International Neuropsychiatric Interview for children and adolescents (MINI-KID; DSM-IV; Sheehan et al., 1998), the inclusion of the questionnaires; Pediatric Quality of Life Scale (PEDS QoL 4.0; Varni et al., 1999), Children's Depression Inventory (CDI; Kovacs & Beck, 1977) and the Family Response Questionnaire (FRQ; Cordingley et al., 2001). Further, we changed the attention task to the Letter Cancellation Task (according to Uttl & Pilkenton-Taylor, 2002) after piloting revealed the previously chosen Trail Making Task was widely used computer game at the time and the inclusion of the five-repetition sit-to-stand task used clinically with adolescents with CFS. A final addition was the collection of saliva samples for cortisol measurement before, during and after the Social Stress task.
- Amendment 2: Addition of school sites to the protocol, use of an adverse events form to assess any events that have recently occurred for the participants, and the inclusion of 3 further questionnaires; the Frost Multidimensional Perfectionism Questionnaire (FMPS, Frost et al., 1990), the Social Phobia and Anxiety Inventory for children (SPAI-c; Beidel, Turner & Morris, 1995) and the Egna Minnen Beträffande Uppfostran (EMBU; Perris et al., 1980). The parents were additionally asked to complete the Affective Style Questionnaire (ASQ; Hofmann & Kashdan, 2010), the Hospital Anxiety and Depression Inventory (HADS; Zigmond & Snaith, 1983) and the Autism Spectrum Quotient (AQ; Baron-Cohen et al., 2001).
- Amendment 3: The chronic illness group was amended from diabetes to asthma.
- Amendment 4: The inclusion of a questionnaire of physiological dysregulation and their attribution during the Social Stress task.
- Amendment 5: Addition of a new site; St. Thomas' Hospital.
- Amendment 6: To recruit asthma patients from local GP surgeries
- Amendment 7: To increase the number of participants followed up to 80.

Appendix 2: Full list of Fukuda criteria

The CDC (Fukuda 1994) Definition for Chronic Fatigue Syndrome

Guidelines for the Evaluation and Study of CFS:

A thorough medical history, physical examination, mental status examination, and laboratory tests must be conducted to identify underlying or contributing conditions that require treatment. Diagnosis or classification cannot be made without such an evaluation. Clinically evaluated, unexplained chronic fatigue cases can be classified as chronic fatigue syndrome if the patient meets both the following criteria:

1. Clinically evaluated, unexplained persistent or relapsing chronic fatigue that is of new or definite onset (i.e., not lifelong), is not the result of ongoing exertion, is not substantially alleviated by rest, and results in substantial reducation in previous levels of occupational, educational, social, or personal activities.

2. The concurrent occurrence of four or more of the following symptoms:

- substantial impairment in short-term memory or concentration;
- sore throat;
- tender lymph nodes;
- muscle pain;
- multi-joint pain without swelling or redness;
- headaches of a new type, pattern, or severity;
- unrefreshing sleep; and
- post-exertional malaise lasting more than 24 hours.

These symptoms must have persisted or recurred during 6 or more consecutive months of illness and must not have predated the fatigue.

Conditions that Exclude a Diagnosis of CFS

1. Any active medical condition that may explain the presence of chronic fatigue, such as untreated hypothyroidism, sleep apnea and narcolepsy, and iatrogenic conditions such as side effects of medication.

2. Some diagnosable illnesses may relapse or may not have completely resolved during treatment. If the persistence of such a condition could explain the presence of chronic fatigue, and if it cannot be clearly established that the original condition has completely resolved with treatment, then such patients should not be classified as having CFS. Examples of illnesses that can present such a picture include some types of malignancies and chronic cases of hepatitis B or C virus infection.

3. Any past or current diagnosis of a major depressive disorder with psychotic or melancholic features;

- bipolar affective disorders

- schizophrenia of any subtype
- delusional disorders of any subtype
- dementias of any subtype
- anorexia nervosa
- or bulemia nervosa

4. Alcohol or other substance abuse, occurring within 2 years of the onset of chronic fatigue and any time afterwards.

5. Severe obesity as defined by a body mass index [body mass index = weight in kilograms ÷ (height in meters)2] equal to or greater than 45. [Note: body mass index values vary considerably among different age groups and populations. No "normal" or "average" range of values can be suggested in a fashion that is meaningful. The range of 45 or greater was selected because it clearly falls within the range of severe obesity.]

Any unexplained abnormality detected on examination or other testing that strongly suggests an exclusionary condition must be resolved before attempting further classification.

Conditions that do not Exclude a Diagnosis of CFS

1. Any condition defined primarily by symptoms that cannot be confirmed by diagnostic laboratory tests, including fibromyalgia, anxiety disorders, somatoform disorders, nonpsychotic or melancholic depression, neurasthenia, and multiple chemical sensitivity disorder.

2. Any condition under specific treatment sufficient to alleviate all symptoms related to that condition and for which the adequacy of treatment has been documented. Such conditions include hypothyroidism for which the adequacy of replacement hormone has been verified by normal thyroid-stimulating hormone levels, or asthma in which the adequacy of treatment has been determined by pulmonary function and other testing.

3. Any condition, such as Lyme disease or syphillis, that was treated with definitive therapy before development of chronic symptoms.

4. Any isolated and unexplained physical examination finding, or laboratory or imaging test abnormality that is insufficient to strongly suggest the existence of an exclusionary condition. Such conditions include an elevated antinuclear antibody titer that is inadequate, without additional laboratory or clinical evidence, to strongly support a diagnosis of a discrete connective tissue disorder.

A Note on the Use of Laboratory Tests in the Diagnosis of CFS

A minimum battery of laboratory screening tests should be performed. Routinely performing other screening tests for all patients has no known value. However, further tests may be indicated on an individual basis to confirm or exclude another diagnosis, such as multiple sclerosis. In these cases, additional tests should be done according to accepted clinical standards.

The use of tests to diagnose CFS (as opposed to excluding other diagnostic possibilities) should be done only in the setting of protocol-based research. The fact that such tests are investigational and do not aid in diagnosis or management should be explained to the patient.

In clinical practice, no tests can be recommended for the specific purpose of diagnosing chronic fatigue syndrome. [Emphasis added.] Tests should be directed toward confirming or excluding other possible clinical conditions. Examples of specific tests that do not confirm or exclude the diagnosis of chronic fatigue syndrome include serologic tests for Epstein-Barr virus, enteroviruses, retroviruses, human herpesvirus 6, and Candida albicans; tests of immunologic function, including cell population and function studies; and imaging studies, including magnetic resonance imaging scans and radionuclide scans (such as single-photon emission computed tomography and positron emission tomography).

From "The Chronic Fatigue Syndrome: A Comprehensive Approach to its Definition and Study". Keiji Fukuda, M.D., M.P.H., Stephen E. Straus, M.D., Ian Hickie, M.D., F.R.A.N.Z.C.P., Michael C. Sharpe, M.R.C.P., M.R.C. Psych., James G. Dobbins, Ph.D., Anthony L. Komaroff, M.D., F.A.C.P. and the International Chronic Fatigue Syndrome Study Group. *Annals of Internal Medicine*, Vol. 121, December 15, 1994, pp. 953-959.

From the CDC's Website on CFS, "CFS Revised Case Definition".

Appendix 3: Information sheet – CFS

Chronic Fatigue Syndrome
Research & Treatment Unit

The Maudsley Hospital
Denmark Hill
London
SE5 8AZ

KING'S College LONDON
University of London

Psycho-Physiological Processes in Chronic Fatigue Syndrome (CFS) in Adolescents.

Information sheet for young person with CFS.

This information sheet tells you about our research project that will help us to understand more about chronic fatigue syndrome (CFS, sometimes known as "ME") in young people. We hope that the results from this research will help us to improve the treatment of this condition. We would like to invite you to help us in our research, if you so wish, and this information sheet is intended to give you enough information to decide whether or not you wish to take part in the study.

We are investigating both physiological and psychological aspects of this condition – in other words, processes in both the body and the mind. In order to help us understand which of these processes are unique to CFS and which are shared with other chronic illnesses, we are comparing these factors in young people with CFS with young people with asthma, and healthy young people. In order to do this, we are asking the young people to undertake several tasks:

1) We will ask you to complete questionnaires about how you feel (these would take about 40 minutes). We would ask you to complete these at home before coming to the Unit.
2) Your accompanying parent will be asked to complete a set of questionnaires whilst you are at the Unit to help us with our investigation.
3) You will be asked to do several tasks to measure different aspects of your functioning; one involves talking, and the others involve looking at words and letters. They only last a few minutes each.
4) Your physiological responses will be assessed by using a measure of skin conductance, cortisol levels and heart rate. Cortisol is a hormone involved in many bodily functions that can be measured in saliva.
5) 2 months after the first stage of the study we will send you a few of the questionnaires you will have completed at the beginning so that we can see whether anything has changed. We will ask you to return these to us in the post. Alternatively you could do this by email or over the phone if preferred.

If you agree to take part in this study, we will send you some questionnaires through the post so that you can get started. When this is complete we will make an appointment for you to come to King's College Hospital for the tasks described above.

This would take place before you come to the unit for treatment, so that we can see how you are feeling before any treatment starts. Taking part in the study is voluntary and you can change your mind at any time; your decision will not affect any ongoing or future healthcare, including any treatment you receive at this unit. All children who participate will receive a £10 HMV gift-card to thank them for their time.

You can decide whether you would like to be involved. We will describe the study and go through this information sheet, which we will then give to you. We will then ask you to sign a consent form to show you have agreed to take part. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

An ethical review of this study has been carried out (Institute of Psychiatry / South London and Maudsley NHS Trust Ethical Committee number 08/H0807/107). The people who will be able to see your questionnaires are those who work in the CFS clinic. The questionnaires will be locked up in a filing cabinet when not in use. If you have any questions please phone Kate Lievesley on 0203 228 5075 or email kate.lievesley@iop.kcl.ac.uk

Thank you very much for your time in considering our study.

Study Number:

Patient Identification Number for this trial:

CONSENT FORM

Title of Project:

Name of Researcher:

Please initial box:

1. I have read and understood the information sheet for the above study. I have had the opportunity to consider the information and ask questions.
□

2. I understand that my taking part in the study is entirely voluntary and that I am free to leave the study at any time without giving a reason.
□

3. I understand that all personal information will be treated as strictly confidential and will not be made public.
□

4. I agree to take part in the above study.
□

5. I agree to my details being kept on file, and to being contacted for follow-up (up to 5 years).
□

6. I agree to giving samples of my saliva during the experimental session at the CFS Unit.
□

_____ _____ _____
Name of Patient Date Signature

_____ _____ _____
Name of Witness Date Signature

Appendix 4: Information sheet – asthma

Chronic Fatigue Syndrome
Research & Treatment Unit

The Maudsley Hospital
Denmark Hill
London
SE5 8AZ

KING'S College LONDON
University of London

Psycho-Physiological Processes in Chronic Fatigue Syndrome (CFS) in Adolescents: Comparison with Asthma

Information sheet for young person who has <u>asthma</u>

This information sheet tells you about our research project. Our research is mainly aimed at improving our understanding and treatment of chronic fatigue syndrome (CFS, sometimes known as "ME") in young people by comparing it with another chronic illness – asthma.

However, we hope this research will also provide further important information about asthma in young people. We would like to invite you to help us in our research, if you so wish, and this information sheet is intended to give you enough information to decide whether or not you wish to take part in the study.

We are investigating both physiological and psychological aspects – in other words, processes in both the body and the mind. To do this, we are asking young people who have asthma, chronic fatigue syndrome or who are healthy young people to undertake several tasks:

1) We will ask you to complete questionnaires about how you feel (these would take about 40 minutes). We would ask you to complete these at home before coming to the Unit.
2) Your accompanying parent will be asked to complete a set of questionnaires whilst you are at the Unit to help us with our investigation.
3) You will be asked to do several tasks to measure different aspects of your functioning; one involves talking, and the others involve looking at words and letters. They only last a few minutes each.
4) Your physiological responses will be assessed by using a measure of skin conductance, cortisol levels and heart rate. Cortisol is a hormone involved in many bodily functions that can be measured in saliva.
5) 2 months after the first stage of the study we will send you a few of the questionnaires you will have completed at the beginning so that we can see whether anything has changed. We will ask you to return these to us in the post. Alternatively you could do this by email or over the phone if preferred.

If you agree to take part in this study, we will send you some questionnaires through the post so that you can get started. When this is complete we will make an appointment for you to come to King's College Hospital for the tasks described above. Taking part in the study is voluntary and you can change your mind at any time; your decision will not affect any ongoing or future healthcare. All children who participate will receive a £10 HMV gift-card to thank them for their time.

You can decide whether you would like to be involved. We will describe the study and go through this information sheet, which we will then give to you. We will then ask you to sign a consent form to show you have agreed to take part. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

An ethical review of this study has been carried out (Institute of Psychiatry / South London and Maudsley NHS Trust Ethical Committee number 08/H0807/107). The people who will be able to see your questionnaires are those who work in the CFS clinic. The questionnaires will be locked up in a filing cabinet when not in use. If you have any questions please phone Kate Lievesley on 0203 228 5075 or email kate.lievesley@kcl.ac.uk

Thank you very much for your time in considering our study.

Appendices

Centre Number:

Study Number:

Patient Identification Number for this trial:

CONSENT FORM

Title of Project:

Name of Researcher:

Please initial box:

1. I have read and understood the information sheet for the above study. I have had the opportunity to consider the information and ask questions.
□

2. I understand that my taking part in the study is entirely voluntary and that I am free to leave the study at any time without giving a reason.
□

3. I understand that all personal information will be treated as strictly confidential and will not be made public.
□

4. I agree to take part in the above study.
□

5. I agree to my details being kept on file, and to being contacted for follow-up (up to 5 years).
□

6. I agree to give samples of my saliva during the experimental session at the CFS Unit.
□

_____ _____ _____
Name of Patient Date Signature

_____ _____ _____
Name of Witness Date Signature

Appendix 5: Contact form

Chronic Fatigue Syndrome
Research & Treatment Unit

The Maudsley Hospital
Denmark Hill
London
SE5 8AZ

KING'S College LONDON
University of London

Contact Information.

Please provide us with the following information:

Child's Name…….

Date of Birth…….

Parent's Name……

Address for correspondence……

……
……
……
……
……

Telephone Number……

Email Address……

Best time to contact……

Thank you very much for your time.

Best wishes,

Kate Lievesley

PhD Student / Research Worker

Appendix 6: Letter to schools for recruitment

Professor Trudie Chalder

CFS Research and Treatment Unit,

Mapother House, 1st Floor,

De Crespigny Park, Denmark Hill,

London.

SE5 8AZ.

Date

Dear **Head teacher**,

Re. Chronic Fatigue Syndrome in adolescents

We are currently working on a project looking at various factors which may contribute to fatigue and disability in chronic fatigue syndrome (CFS) in adolescents. We intend to do this by using both questionnaire and experimental tasks, comparing young people with CFS with age-matched young people with diabetes, and healthy adolescents. I am contacting you with regard to your school's possible involvement in our study.

Individuals with CFS experience profound fatigue with a minimum duration of 6 months. Such fatigue cannot be alleviated by rest, with many young people having long periods of school non-attendance, resulting in disrupted education and loss of peer relationships. Further symptoms include muscle pain, sleep disturbance and both memory/concentration problems are commonly reported. The incidence of CFS is higher than that of asthma, type I diabetes or anxiety disorders amongst adolescents. It is therefore critical that this condition be treated as quickly and effectively as possible to reduce the immediate suffering and disability and to prevent longer-term adverse consequences.

In particular, I would be very grateful if you would be willing to hand out information sheets about our study to children at your school, between the ages of 11 and 18years. Please find attached a copy of our information sheets for your information. This will then allow the children and their parents to discuss whether our study would be of interest to them.

I would appreciate any assistance you may be able to provide. Please do not hesitate to contact the research team for any further information: kate.lievesley@kcl.ac.uk

Yours truly,

Kate Lievesley

PhD Student

Institute of Psychiatry, KCL

Appendix 7: Information sheet – healthy controls

Chronic Fatigue Syndrome
Research & Treatment Unit

The Maudsley Hospital
Denmark Hill
London
SE5 8AZ

KING'S College LONDON
University of London

Psycho-Physiological Processes in Chronic Fatigue Syndrome (CFS) in Adolescents.

Information sheet for young person who has <u>never experienced</u> CFS.

This information sheet tells you about our research project that will help us to understand more about Chronic Fatigue Syndrome (CFS, sometimes known as "ME") in young people. For this research we need to compare CFS sufferers with other <u>young people who have never experienced CFS</u>. We hope that the results from this research will help us to improve the treatment of this condition.

We would like to invite you to help us in our research, if you so wish, and this information sheet is intended to give you enough information to decide whether or not you wish to take part in the study.

We are investigating both physiological and psychological aspects of this condition – in other words, processes in both the body and the mind. To do this, we are asking young people who have never experienced Chronic Fatigue Syndrome to undertake several tasks. Their performance will then be compared to that of young people suffering from Chronic Fatigue Syndrome. The tasks are:

1) We will ask you to complete questionnaires about how you feel (these would take about 30 minutes). We would ask you to complete these at home before the task session.
2) Parents are also asked to complete a questionnaire booklet.
3) You will be asked to do several tasks to measure different aspects of your functioning; one involves talking, and the others involve looking at words and letters. They only last a few minutes each.
4) Your physiological responses will be assessed by using a measure of skin conductance, cortisol levels and heart rate. Cortisol is a hormone involved in many bodily functions that can be measured in saliva.
5) 2 months after the first stage of the study we will send you a few of the questionnaires you will have completed at the beginning so that we can see whether anything has changed. We will ask you to return these to us in the post. Alternatively you could do this by email or over the phone if preferred.

If you agree to take part in this study, we will send you some questionnaires through the post so that you can get started. When this is complete we will make an appointment for the researcher to see you at school at a time agreed by the school for the one-off task session.

Taking part in the study is voluntary and you can change your mind at any time; your decision will not affect any ongoing or future healthcare. All children who participate will receive a £10 HMV gift-card to thank them for their time.

You can decide whether you would like to be involved. We will describe the study and go through this information sheet, which we will then give to you. We will then ask you to sign a consent form to show you have agreed to take part. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

An ethical review of this study has been carried out (Institute of Psychiatry / South London and Maudsley NHS Trust Ethical Committee number 08/H0807/107). The people who will be able to see your questionnaires are those who work in the CFS clinic. The questionnaires will be locked up in a filing cabinet when not in use. If you have any questions please phone Kate Lievesley on 0203 228 5075 or email kate.lievesley@kcl.ac.uk

Thank you very much for your time in considering our study.

Appendix 8: Self-report questionnaires (child)

Name:

Date of Birth:

CHRONIC FATIGUE SYNDROME
QUESTIONNAIRE PACK
FOR YOUNG PERSON WITH CFS

Thank you for agreeing to participate in this study. We are very interested in finding out more about your illness and the impact the symptoms have had on your life.

This booklet contains a number of questions about the nature of your symptoms, how you manage these symptoms and the impact these have had on your physical health and psychological well-being

There are no right or wrong answers to these questions. We are most interested in your own personal views rather than those of your family or the people who are treating you.

We ask you to answer the questions as honestly and as quickly as possible.

If you find it hard to keep your mind on the statements, take a short break. The questionnaire may be completed over a day or two.

This questionnaire is completely

CONFIDENTIAL.

Thank you very much for your time

Demographic Information

NAME: ……..

Date of birth:

☐ ☐ / ☐

Age:

☐ Years ☐ Months

Gender:

Male ☐

Female ☐

Ethnicity: ……..

Main carer:

Both parents↑ □

Mother↑ □

Father □

Grandparents↑ □

Other member of the family □

(please specify)

……

Foster parents/Adoptive parents↑ □

Other↑ □

(please specify)

……

CFS DIAGNOSTIC CRITERIA

Do you suffer from severe fatigue (either persistent or relapsing)

0 no (go to question 7) ☐

0 mild fatigue ☐

1 moderate fatigue ☐

1 severe fatigue ☐

2. Do you suffer from physical and mental fatigue?

physical only ☐

mental only ☐

physical and mental fatigue ☐

3. On average, how much of the time do you feel fatigued?

0 less than 50% of the time ☐

1 50% of the time or more ☐

4. How long have you been feeling severely fatigued like this?

0 less than 6 months ☐

1 6 months or more ☐

5. Does the fatigue substantially impair any of the following areas:

Work ☐

Study ☐

Physical exercise ☐

Housework and home management ☐

Self-care (dressing/bathing/preparing simple meals) ☐

Leisure activities ☐

Family life/childcare ☐

6. Would you say the fatigue is disabling?

0 no ☐

1 yes ☐

7. Does the fatigue go or get substantially better if you rest?

0 yes ☐

1 no ☐

8. Do you suffer from any of the following symptoms?

Muscle pain	☐	Malaise for 24 hours or more after exertion	☐
Joint pain	☐	Poor memory	☐
Headaches	☐	Poor concentration	☐
Tender neck/armpit glands	☐	Unrefreshing sleep	☐
Sore throat	☐		

CFS

1. How long ago did you notice the onset of your fatigue?

2. Which of the following best describes the cause of your symptoms? (tick as many boxes as apply):

Environment	☐	Stress	☐
Problems at school	☐	Family problems	☐
Problems with friends	☐	Virus	☐
Not enough exercise	☐	Too much exercise	☐

3. How long do you think it will take you to recover from CFS?

☐ Up to a month ☐ 4-8 months ☐ Don't Know

☐ 2 months ☐ 8-12 months

☐ 2- 4 months ☐ More than12months

4. Does/Has anyone in your family suffer/suffered from CFS? YES ☐

NO ☐

5. What is your current average weekly school/college attendance:

…….full days ……..half days

EXERCISE

1. Did you usually, before you became ill with CFS, do any regular form of exercise or sport?

YES ☐

NO ☐

IF YES: What exercise did you do, and how often did you do this?

IF NO, Did you usually, before you had CFS, do any activity, at least once a week that made you work up a sweat?

☐ NO ☐ Twice a week ☐ 4 times a week ☐ 6 times a week

☐ Yes –Once a week ☐ 3 times a week ☐ 5 times a week ☐ 7 or more times a week

2. What do you do now as a regular form of exercise or sport?

……
……
……

MEDICAL HISTORY

1. Please give details of any other current medical problems:

2. Are you currently seeing the doctor or attending a hospital for any medical problems other than CFS?

☐ NO

☐ YES

IF YES please give details:

3. Have you had any other medical problems in the past, not yet mentioned?

4. Have you had any operations in the past?

☐ NO

☐ YES

IF YES please give details:

5. Do you have/ Have you had any allergies? No / Yes (please give details)

6. Are you taking any medication at the moment? No / Yes (please give details)

7. Have you taken any other medication in the past? No / Yes (please give details)

If female:

Have you started your periods? Yes ☐

No ☐

IF YES:

How old were you when you had your first period?

Are your periods regular? Yes ☐ No ☐

C.F.Q. We would like to know whether or not you have been having any problems with feeling tired, weak or lacking in energy in the last few weeks. Please answer ALL the questions simply by TICKING the answer which you think most nearly applies to you. We would like to know how you feel either at the moment or recently, rather than a long time ago. If you have been feeling tired for a long time, we want you to compare yourself to how you felt when last well.

Do you have problems with tiredness?	Less than usual ☐	No more than usual ☐	More than usual ☐	Much more than usual ☐
Do you need to rest more?	Less than usual ☐	No more than usual ☐	More than usual ☐	Much more than usual ☐
Do you feel sleepy or drowsy?	Less than usual ☐	No more than usual ☐	More than usual ☐	Much more than usual ☐
Do you have problems starting things?	Less than usual ☐	No more than usual ☐	More than usual ☐	Much more than usual ☐
Do you lack energy?	Better than usual ☐	No more than usual ☐	More than usual ☐	Much more than usual ☐
Do you have less strength in your muscles?	Better than usual ☐	No more than usual ☐	More than usual ☐	Much more than usual ☐
Do you feel weak?	Less than usual ☐	Same as usual ☐	More than usual ☐	Much more than usual ☐
Do you have difficulty concentrating?	Less than usual ☐	Same as usual ☐	More than usual ☐	Much more than usual ☐

Do you make slips of the tongue when speaking?	Less than usual ☐	No more than usual ☐	More than usual ☐	Much more than usual ☐
Do you find it more difficult to find the correct word?	Less than usual ☐	No more than usual ☐	More than usual ☐	Much more than usual ☐
How is your memory?	Better than usual ☐	No worse than usual ☐	Worse than usual ☐	Much worse than usual ☐

The next questions ask about <u>muscle pain</u>.

Do your muscles hurt at rest?	Less than usual ☐	No more than usual ☐	Worse than usual ☐	Much worse than usual ☐
Do your muscles hurt after exercise?	Less than usual ☐	No more than usual ☐	Worse than usual ☐	Much worse than usual ☐

If you are tired at the moment, please indicate approximately how long this has lasted.

I am not tired ☐

Less than 1 week ☐

Less than 3 months ☐

Between 3 & 6 months ☐

6 months or more ☐

Overall, what percentage of the time do you feel tired?

0% of the time ☐

25% of the time ☐

50% of the time ☐

75% of the time ☐

All of the time ☐

S.F.36

Please tick the box that most applies to you. Please be sure to answer all questions.

Activity	Yes, limited a lot	Yes, limited a little	No, not limited at all
Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐	☐	☐
Moderate activities such as moving a table, pushing a vacuum cleaner, bowling or playing golf	☐	☐	☐
Lifting or carrying groceries	☐	☐	☐
Climbing several flights of stairs	☐	☐	☐
Climbing one flight of stairs	☐	☐	☐
Bending, kneeling or stooping	☐	☐	☐
Walking more than a mile	☐	☐	☐
Walking several hundred yards	☐	☐	☐
Walking one hundred yards	☐	☐	☐
Bathing or dressing yourself	☐	☐	☐

W.S.A.S.

Please circle the number which best describes how you feel about each of these statements.

Because of my illness my ability to attend school/college/work is impaired

0 1 2 3 4 5 6 7 8

Not at all Slightly Definitely Markedly Very severely

Because of my illness my ability to do homework is impaired

0 1 2 3 4 5 6 7 8

Not at all Slightly Definitely Markedly Very severely

Because of my illness my social leisure activities are impaired (with other people e.g. parties, outings, seeing friends)

0 1 2 3 4 5 6 7 8

Not at all Slightly Definitely Markedly Very severely

Because of my illness my private leisure activities are impaired (done alone, e.g., reading, watching t.v., listening to music)

0 1 2 3 4 5 6 7 8

Not at all Slightly Definitely Markedly Very severely

Because of my illness my ability to make friends is impaired

0 1 2 3 4 5 6 7 8

Not at all Slightly Definitely Markedly Very severely

C.A.P.S.

This is a chance to find out about yourself. It is not a test. There are no right answers and everyone will have different answers. Be sure that your answers show how you actually are.

When you are ready to begin, read each sentence and pick your answer by circling a number from 1 to 5. The five possible answers for each sentence are listed below:

1	False- Not true at all of me.
2	Mostly false
3	Neither true nor false
4	Mostly true
5	Very true of me

For example, if you were given the sentence "I like to read comic books", you would circle "5" if this is very true of you. If you were given the sentence "I like to keep my room neat and tidy", you would circle "1" if this was false and not true of you at all.

Please be sure to answer ALL of the sentences:

		False				True
1	I try to be perfect in everything I do	1	2	3	4	5
2	I want to be the best at everything I do	1	2	3	4	5
3	My parents don't always expect me to be perfect in everything I do	1	2	3	4	5
4	I feel that I have to do my best all the time	1	2	3	4	5
5	There are people in my life who expect me to be perfect	1	2	3	4	5
6	I always try for the top score on a test	1	2	3	4	5
7	It really bothers me if I don't do my best all the time	1	2	3	4	5
8	My family expects me to be perfect	1	2	3	4	5
9	I don't always try to be the best	1	2	3	4	5
10	People expect more from me than I am able to give	1	2	3	4	5
11	I get mad at myself when I make a mistake	1	2	3	4	5
12	Other people think I have failed if I do not do my very best all the time	1	2	3	4	5

13	Other people always expect me to be perfect	1	2	3	4	5
14	I get upset if there is even one mistake in my work	1	2	3	4	5
15	People around me expect me to be great at everything	1	2	3	4	5
16	When I do something, it has to be perfect	1	2	3	4	5
17	My teachers expect my work to be perfect	1	2	3	4	5
18	I do not have to be the best at everything I do	1	2	3	4	5
19	I am always expected to do better than others	1	2	3	4	5
20	Even when I pass, I feel that I have failed if I didn't get one of the highest marks in the class	1	2	3	4	5
21	I feel that people ask too much of me	1	2	3	4	5
22	I can't stand to be less than perfect	1	2	3	4	5

S.D.S(Children)

This questionnaire lists a number of experiences that most children have at one time or another. Read each of these carefully. After you have read one, decide whether it does or does not fit you. Please tick either True or False according to which is most appropriate for you. If you have any questions at any time, the question can be explained to you by our researcher.

	True	False
I always enjoy myself at a party.	☐	☐
I tell a little lie sometimes.	☐	☐
I never get angry if I have to stop in the middle of something I'm doing to eat dinner, or go to school.	☐	☐
Sometime I don't like to share my things with my friends.	☐	☐
I am always respectful of older people.	☐	☐
I would never hit a boy or girl who was smaller than me.	☐	☐
Sometimes I do not feel like doing what my teachers tell me to do.	☐	☐
I never act "fresh" or "talk back" to my mother or father.	☐	☐
When I make a mistake, I always admit I am wrong.	☐	☐
I feel my parents do not always show good judgements.	☐	☐
I have never felt like saying unkind things to a person.	☐	☐
I always finish all of my homework on time.	☐	☐
Sometimes I have felt like throwing or breaking things.	☐	☐
I never let someone else get blamed for what I did wrong.	☐	☐
Sometimes I say something just to impress my friends	☐	☐
I am always careful about keeping my clothing neat, and my room picked up.	☐	☐
I never shout when I feel angry.	☐	☐
Sometimes I feel like staying home from school even if	☐	☐

I am not sick.		
Sometimes I wish that my parents didn't check up on me so closely.	☐	☐
I always help people who need help.	☐	☐
Sometimes I argue with my mother to do something she doesn't want me to.	☐	☐
I never say anything that would make a person feel bad.	☐	☐
My teachers always know more about everything than I do.	☐	☐
I am always polite, even to people who are not very nice.	☐	☐
Sometimes I do things I've been told not to do.	☐	☐
I never get angry.	☐	☐
I sometimes want to things just because my friends have them.	☐	☐
I always listen to my parents.	☐	☐
I never forget to say "please" and "thank you".	☐	☐
Sometimes I wish I could just "mess around" instead of having to go to school	☐	☐
I always wash my hands before every meal.	☐	☐
Sometimes I dislike helping my parents even though I know they need my help around the house.	☐	☐
I never find it hard to make friends.	☐	☐
I have never been tempted to break a rule or a law.	☐	☐
Sometimes I try to get even when someone does something to me I don't like.	☐	☐
I sometimes feel angry when I don't get my way.	☐	☐
I always help an injured animal.	☐	☐
Sometimes I want to do things my parents think I am too young to do.	☐	☐
I sometimes feel like making fun of other people.	☐	☐
I have never borrowed anything without asking permission first.	☐	☐
Sometimes I get annoyed when someone disturbs	☐	☐

something I've been working on.		
I am always glad to cooperate with others.	☐	☐
I never get annoyed when my best friend wants to do something I don't want to do.	☐	☐
Sometimes I wish that other kids would pay more attention to what I say.	☐	☐
I always do the right things.	☐	☐
Sometimes I don't like to obey my parents.	☐	☐
Sometimes I don't like it when another person asks me to do things for him.	☐	☐
Sometimes I get mad when people don't do what I want.	☐	☐

B.E.S.

Please read each statement below and decide how well it describes how you have felt over the past six months. Please indicate your answer by placing a tick under the column that best describes what you think. To decide whether a given answer has been typical of your way of looking at things over the past six months, simply keep in mind what you are like most of the time.

	Totally agree	Agree very much	Agree slightly	Neutral	Disagree slightly	Disagree very much	Totally disagree
It is a sign of weakness if I have miserable thoughts.	☐	☐	☐	☐	☐	☐	☐
If I have difficulties I should not admit them to others.	☐	☐	☐	☐	☐	☐	☐
If I lose control of my emotions in front of others, they will think less of me.	☐	☐	☐	☐	☐	☐	☐

I should be able to control my emotions.	☐	☐	☐	☐	☐	☐	☐
If I am having difficulties it is important to put on a brave face.	☐	☐	☐	☐	☐	☐	☐
If I show signs of weakness then others will reject me.	☐	☐	☐	☐	☐	☐	☐
I should not let myself give in to negative feelings.	☐	☐	☐	☐	☐	☐	☐
I should be able to cope with difficulties on my own without turning to others for support.	☐	☐	☐	☐	☐	☐	☐
To be acceptable to others, I must keep any difficulties or negative feelings to myself.	☐	☐	☐	☐	☐	☐	☐
It is stupid to have miserable thoughts.	☐	☐	☐	☐	☐	☐	☐
It would be a sign of weakness to show my emotions in public.	☐	☐	☐	☐	☐	☐	☐
Others expect me to always be in control of my emotions.	☐	☐	☐	☐	☐	☐	☐

C.B.R.Q.Please indicate how much you agree or disagree with the following statements about your current symptoms by ticking the appropriate box.

VIEWS ABOUT YOUR SYMPTOMS	STRONGLY DISAGREE	DISAGREE	NEITHER AGREE NOR DISAGREE	AGREE	STRONGLY AGREE
I am afraid that I will make my symptoms worse if I exercise	☐	☐	☐	☐	☐
My symptoms would be relieved if I were to exercise	☐	☐	☐	☐	☐
Avoiding unnecessary activities is the safest thing I can do to prevent my symptoms from worsening	☐	☐	☐	☐	☐
The severity of my symptoms must mean there is something serious going on in my body	☐	☐	☐	☐	☐
Even though I experience symptoms, I don't think they are actually harming me	☐	☐	☐	☐	☐
When I experience symptoms, my body is telling me that there is something seriously wrong.	☐	☐	☐	☐	☐
Physical activity makes my symptoms worse	☐	☐	☐	☐	☐
Doing less helps symptoms	☐	☐	☐	☐	☐
Symptoms are a signal that I am damaging myself	☐	☐	☐	☐	☐
I am afraid I will have more symptoms if I am not careful	☐	☐	☐	☐	☐
I should avoid exercise when I have symptoms	☐	☐	☐	☐	☐
I worry that I may become permanently bedridden because of my symptoms	☐	☐	☐	☐	☐

I think that if my symptoms get too severe they may never decrease	☐	☐	☐	☐	☐
My illness is awful and I feel that it overwhelms me	☐	☐	☐	☐	☐
I will never feel right again	☐	☐	☐	☐	☐
When I experience symptoms, I think about them constantly	☐	☐	☐	☐	☐
I worry when I am experiencing symptoms	☐	☐	☐	☐	☐
When I am experiencing symptoms it is difficult for me to think of anything else	☐	☐	☐	☐	☐
I think a great deal about my symptoms	☐	☐	☐	☐	☐
My symptoms are always at the back of my mind	☐	☐	☐	☐	☐
I spend a lot of time thinking about my illness	☐	☐	☐	☐	☐
I am embarrassed about my symptoms	☐	☐	☐	☐	☐
I worry that people will think badly of me because of my symptoms	☐	☐	☐	☐	☐
The embarrassing nature of my symptoms prevents me from doing things	☐	☐	☐	☐	☐
I avoid social situations because I am scared my symptoms will get out of control	☐	☐	☐	☐	☐
I am ashamed of my symptoms	☐	☐	☐	☐	☐
My symptoms have the potential to make me look foolish in front of other people	☐	☐	☐	☐	☐

Appendices

We are interested in how you respond to or manage your symptoms at the moment. Listed below are a number of different responses that people may have to their symptoms.

Please indicate how often you respond in the following ways by ticking the appropriate box. Choose the most accurate answer for YOU, not what you think "most people" would say or do.

MANAGING SYMPTOMS	Never	Some-times	Quite often	Very Often	All the time
I stay in bed to control my symptoms	☐	☐	☐	☐	☐
When I experience symptoms, I rest.	☐	☐	☐	☐	☐
I tend to avoid activities that make my symptoms worse	☐	☐	☐	☐	☐
I tend to nap during the day to control my symptoms	☐	☐	☐	☐	☐
I tend to overdo things when I feel energetic	☐	☐	☐	☐	☐
I find myself rushing to get things done before I crash	☐	☐	☐	☐	☐
I tend to overdo things and then rest up for a while	☐	☐	☐	☐	☐
I tend to do a lot on a good day and rest on a bad day	☐	☐	☐	☐	☐
I sleep when I'm tired in order to control my symptoms	☐	☐	☐	☐	☐
I avoid making social arrangements in case I'm not up to it.	☐	☐	☐	☐	☐
I avoid exerting myself in order to control my symptoms	☐	☐	☐	☐	☐
I'm a bit all or nothing when it comes to doing things	☐	☐	☐	☐	☐
I avoid stressful situations	☐	☐	☐	☐	☐

STAI

A number of statements which people have used to describe themselves are given below. Read each statement and then tick the appropriate box to the right of the statement to indicate how you generally feel. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe how you generally feel.

	Almost never	Sometimes	Often	Almost Always
1. I feel calm	☐	☐	☐	☐
2. I feel secure	☐	☐	☐	☐
3. I am tense	☐	☐	☐	☐
4. I feel strained	☐	☐	☐	☐
5. I feel at ease	☐	☐	☐	☐
6. I feel upset	☐	☐	☐	☐
7. I am presently worrying over possible misfortunes	☐	☐	☐	☐
8. I feel satisfied	☐	☐	☐	☐
9. I feel frightened	☐	☐	☐	☐
10. I feel comfortable	☐	☐	☐	☐
11. I feel self-confident	☐	☐	☐	☐
12. I feel nervous	☐	☐	☐	☐
13. I am jittery	☐	☐	☐	☐
14. I feel indecisive	☐	☐	☐	☐
15. I am relaxed	☐	☐	☐	☐
16. I feel content	☐	☐	☐	☐
17. I am worried	☐	☐	☐	☐
18. I feel confused	☐	☐	☐	☐
19. I feel steady	☐	☐	☐	☐
20. I feel pleasant	☐	☐	☐	☐
21. I feel pleasant	☐	☐	☐	☐
22. I feel nervous and restless	☐	☐	☐	☐
23. I feel satisfied	☐	☐	☐	☐

with myself				
24. I wish I could be as happy as others seem to be	☐	☐	☐	☐
25. I feel like a failure	☐	☐	☐	☐
26. I feel rested	☐	☐	☐	☐
27. I am “calm, cool and collected”	☐	☐	☐	☐
28. I feel that difficulties are piling up so that I cannot overcome them	☐	☐	☐	☐
29. I worry too much over something that really doesn’t matter	☐	☐	☐	☐
30. I am happy	☐	☐	☐	☐
31. I have disturbing thoughts	☐	☐	☐	☐
32. I lack self-confidence	☐	☐	☐	☐
33. I feel secure	☐	☐	☐	☐
34. I make decisions easily	☐	☐	☐	☐
35. I feel inadequate	☐	☐	☐	☐
36. I am content	☐	☐	☐	☐
37. Some unimportant thought runs through my mind and bothers me	☐	☐	☐	☐
38. I take disappointments so keenly that I can’t put them out of my mind	☐	☐	☐	☐
39. I am a steady person	☐	☐	☐	☐
40. I get into a state of tension or turmoil as I think over my recent concerns and interests	☐	☐	☐	☐

I.S.

Please complete this questionnaire by ticking the box that most applies to you, for each of these questions. Please ensure you answer all questions.

	0	1	2	3	4
	No	A little	Moderate	Much	Very much
I find it difficult to get to sleep	☐	☐	☐	☐	☐
My sleep is interrupted and disturbed	☐	☐	☐	☐	☐
I wake up many times during my sleep	☐	☐	☐	☐	☐
I wake up early in the morning before getting enough sleep	☐	☐	☐	☐	☐
I feel depressed when it is time for me to go to bed	☐	☐	☐	☐	☐
Before I fall asleep I have bad thoughts	☐	☐	☐	☐	☐
I feel tired when I wake up	☐	☐	☐	☐	☐
I normally wake up in a bad mood	☐	☐	☐	☐	☐
I get tense when I wake up	☐	☐	☐	☐	☐
My interrupted sleep annoys me	☐	☐	☐	☐	☐
My interrupted sleep affects my relationships with others	☐	☐	☐	☐	☐
My interrupted sleep affects my work performance	☐	☐	☐	☐	☐

EPQ-R (Short Form)

Please answer ALL of the questions, CIRCLING the answer you feel best describes you. Answer the questions honestly and do not spend too much time thinking about them.

1. Does your mood often go up and down?.....YES NO

2. Are you a talkative person?.....YES NO

3. Do you ever feel 'just miserable' for no reason?.....YES NO

4. Are you rather lively?.....YES NO

5. Are you an irritable person?..... YES NO

6. Do you enjoy meeting new people?.....YES NO

7. Are your feelings easily hurt?..... YES NO

8. Can you usually let yourself go and enjoy yourself at a lively party?..YES NO

9. Do you often feel 'fed-up'?..... YES NO

10. Do you usually take initiative in making new friends?.....YES NO

11. Would you call yourself a nervous person?.....YES NO

12. Can you easily get some life into a rather dull party?.....YES NO

13. Are you a worrier?..... YES NO

14. Do you tend to keep in the background on social occasions?.....YES NO

15 Would you call yourself tense or 'highly-strung'?.....YES NO

16 Do you like mixing with people?..... YES NO

17 Do you worry too long after an embarrassing experience?.....YES NO

18. Do you like plenty of bustle and excitement around you?.....YES NO

19 Do you suffer from 'nerves'?.....YES NO

20 Are you mostly quiet when you are with other people?.....YES NO

21 Do you often feel lonely?..... YES NO

22 Do other people think of you as being very lively?.....YES NO

23 Are you often troubled about feelings of guilt?.....YES NO

24 Can you get a party going?..... YES NO

Appendices

E.A.T

Please Circle a Response for Each of the Following Statements:

Question	Always	Usually	Often	Sometimes	Rarely	Never
1. Am terrified about being overweight	3	2	1	0	0	0
2. Avoid eating when I am hungry.	3	2	1	0	0	0
3. Find myself preoccupied with food.	3	2	1	0	0	0
4. Have gone on eating binges where I feel I may not be able to stop.	3	2	1	0	0	0
5. Cut my food into small pieces.	3	2	1	0	0	0
6. Aware of the calorie content of foods I eat.	3	2	1	0	0	0
7. Particularly avoid food with a high carbohydrate content (bread, rice, potatoes, etc.)	3	2	1	0	0	0
8. Feel that others would prefer if I ate more.	3	2	1	0	0	0
9. Vomit after I have eaten.	3	2	1	0	0	0
10. Feel extremely guilty after eating	3	2	1	0	0	0
11. Am preoccupied with a desire to be thinner.	3	2	1	0	0	0
12. Think about burning up calories when I exercise.	3	2	1	0	0	0
13. Other people think I'm too thin.	3	2	1	0	0	0
14. Am preoccupied with the thought of having fat on my body.	3	2	1	0	0	0
15. Take longer than others to eat my meals	3	2	1	0	0	0

16. Avoid foods with sugar in them.	3	2	1	0	0	0
17. Eat diet foods.	3	2	1	0	0	0
18. Feel that food controls my life.	3	2	1	0	0	0
19. Display self-control around food.	3	2	1	0	0	0
20. Feel that other pressure me to eat.	3	2	1	0	0	0
21. Give too much time and thought to food.	3	2	1	0	0	0
22. Feel uncomfortable after eating sweets.	3	2	1	0	0	0
23. Engage in dieting behavior.	3	2	1	0	0	0
24. Like my stomach to be empty.	3	2	1	0	0	0
25. Have the impulse to vomit after meals.	3	2	1	0	0	0
26. Enjoy trying new rich foods.	0	0	0	1	2	3

Please respond to each of the following questions:

1. Have you gone on eating binges where you feel that you may not be able to stop?

   (Eating much more than most people would eat under the circumstances). No ☐ YES ☐

   If YES, on average, how many times per month in the last 6 months? ☐

   2. Have you ever made yourself sick (vomited) to control your weight or shape? No ☐ YES ☐

   If YES, on average, how many times per month in the last 6 months? ☐

   3. Have you ever used laxatives, diet pills or diuretics (water pills) to control your weight or shape? No ☐ YES ☐

   If YES, on average, how many times per month in the last 6 months? ☐

   4. Have you ever been treated for an eating disorder? No ☐ YES ☐ If YES, when? ☐

   5. Have you recently thought of or attempted suicide? No ☐ YES ☐ , If YES, when? ☐

FMPS. Please circle the number that best corresponds to your agreement with each statement below.	Strongly disagree				Strongly agree
1. My parents set very high standards for me.	1	2	3	4	5
2. Organisation is very important to me.	1	2	3	4	5
3. As a child, I was punished for doing things less than perfectly.	1	2	3	4	5
4. If I do not set the highest standards for myself, I am likely to end up a second-rate person.	1	2	3	4	5
5. My parents never tried to understand my mistakes.	1	2	3	4	5
6. It is important to me that I be thoroughly competent in everything I do.	1	2	3	4	5
7. I am a neat person.	1	2	3	4	5
8. I try to be an organised person.	1	2	3	4	5
9. If I fail at work / school, I am a failure as a person.	1	2	3	4	5
10. I should be upset if I make a mistake.	1	2	3	4	5
11. My parents wanted me to be the best at everything.	1	2	3	4	5
12. I set higher goals than most people.	1	2	3	4	5
13. If someone does a task at work / school better than I, then I feel like I failed the whole task.	1	2	3	4	5
14. If I fail partly, it is as bad as being a complete failure.	1	2	3	4	5
15. Only outstanding performance is good enough in my family.	1	2	3	4	5
16. I am very good at focusing my efforts on attaining a goal.	1	2	3	4	5
17. Even when I do something very carefully, I often feel that it is not quite right.	1	2	3	4	5
18. I hate being less than best at things.	1	2	3	4	5
19. I have extremely high goals.	1	2	3	4	5
20. My parents have expected excellence from me.	1	2	3	4	5
21. People will probably think less of me if I make a mistake.	1	2	3	4	5
22. I never felt like I could meet my parents' expectations.	1	2	3	4	5
23. If I do not do as well as other people, it means I am an inferior human being.	1	2	3	4	5
24. Other people seem to accept lower standards from themselves than I do.	1	2	3	4	5

25. If I do not do well all the time, people will not respect me.	1	2	3	4	5
26. My parents have always had higher expectations for my future than I have.	1	2	3	4	5
27. I try to be a neat person.	1	2	3	4	5
28. I usually have doubts about the simple everyday things I do.	1	2	3	4	5
29. Neatness is very important to me.	1	2	3	4	5
30. I expect higher performance in my daily tasks than most people.	1	2	3	4	5
31. I am an organised person.	1	2	3	4	5
32. I tend to get behind in my work because I repeat things over and over.	1	2	3	4	5
33. It takes me a long time to do something 'right'.	1	2	3	4	5
34. The fewer mistakes I make, the more people will like me.	1	2	3	4	5
35. I never felt like I could meet my parents' standards.	1	2	3	4	5

In the past ONE month, how much of a problem has this been for you…

ABOUT MY HEALTH AND ACTIVITIES (PROBLEMS WITH)	Never	Almost never	Some-times	Often	Almost always
1. It is hard for me to walk more than one block	0	1	2	3	4
2. It is hard for me to run	0	1	2	3	4
3. It is hard for me to do sports activities or exercise	0	1	2	3	4
4. It is hard for me to lift something heavy	0	1	2	3	4
5. It is hard for me to take a bath or shower by myself	0	1	2	3	4
6. It is hard for me to do chores around the house	0	1	2	3	4
7. I hurt or ache	0	1	2	3	4
8. I have low energy	0	1	2	3	4

Appendices

ABOUT MY FEELINGS	Never	Almost never	Some-times	Often	Almost always
1. I feel afraid or scared	0	1	2	3	4
2. I feel sad or blue	0	1	2	3	4
3. I feel angry	0	1	2	3	4
4. I have trouble sleeping	0	1	2	3	4
5. I worry about what will happen to me	0	1	2	3	4

HOW I GET ALONG WITH OTHERS	Never	Almost never	Some-times	Often	Almost always
1. I have trouble getting along with other kids	0	1	2	3	4
2. other kids do not want to be my friend	0	1	2	3	4
3. other kids tease me	0	1	2	3	4
4. I cannot do things that other kids my age can do	0	1	2	3	4
5. It is hard to keep up when I play with other kids	0	1	2	3	4

ABOUT SCHOOL	Never	Almost never	Some-times	Often	Almost always
1. It is hard to pay attention in class	0	1	2	3	4
2. I forget things	0	1	2	3	4
3. I have trouble keeping up with my school work	0	1	2	3	4
4. I miss school because of not feeling well	0	1	2	3	4
5. I miss school to go to the doctors or hospital	0	1	2	3	4

SPAI-c: Please answer the following questionnaire, ticking the box that most applies to you.	Never or hardly ever	Sometimes	Most of the time or always
1. I feel scared when I have to join in a social situation with a large group of boys and girls (more than 6)			
2. I feel scared when I am with other boys and girls or adults and I become the centre of attention (they all look at me)			
3. I feel scared when I am with other boys and girls or adults and I have to do something while they watch me (read aloud, play a game, play a sport)			
4. I feel scared when I have to speak or read in front of a group of people			
5. I feel scared when answering questions in class or at meetings even when I know the answer			
6. I feel so scared at parties, dances, school or anyplace where there will be more than two other people that I go home early			
7. I feel scared when I meet new kids			
8. I am too scared to ask questions in class			
9. I feel scared when I am in the school cafeteria with			
Boys or girls my age that I know			
Boys or girls my age that I don't know			
Adults			
10. If somebody starts arguing with me, I feel scared and do not know what to do if that person is			
A boy or girl my age who I know			
A boy or girl my age who I don't know			
An adult			
11. If somebody asks me to do something that I don't want to do, I feel scared and don't know what to say if that person is			
A boy or girl my age who I know			
A boy or girl my age who I don't know			

An adult			
12. I feel scared and don't know what to do when in an embarrassing situation with (embarrassed means that your face gets hot and red)			
A boy or girl my age who I know			
A boy or girl my age who I don't know			
An adult			
13. if somebody says something that I think is wrong or bad, I feel scared saying what I think if that person is			
A boy or girl my age who I know			
A boy or girl my age who I don't know			
An adult			
14. I feel scared when I start to talk to			
Boys or girls my age that I know			
Boys or girls my age that I don't know			
Adults			
15. I feel scared if I have to talk for longer than a few minutes with			
Boys or girls my age that I know			
Boys or girls my age that I don't know			
Adults			
16. I feel scared when speaking (giving a book report, reading in front of class) in front of			
Boys or girls my age that I know			
Boys or girls my age that I don't know			
Adults			
17. I feel cared when in a school play, choir, music, or dance recital in front of			
Boys or girls my age that I know			
Boys or girls my age that I don't know			
Adults			
18. I feel scared when I am ignored or made fun of by			

Boys or girls my age that I know			
Boys or girls my age that I don't know			
Adults			
19. I try to avoid social situations (parties, school, playing with others) where there are			
Boys or girls my age that I know			
Boys or girls my age that I don't know			
Adults			
20. I leave social situations (parties, school, playing with others) where there are			
Boys or girls my age that I know			
Boys or girls my age that I don't know			
Adults			
21. Before going to a party or going someplace with others, I think about what might go wrong. I think			
Will I make a mistake and look stupid?			
What if nobody talks to me?			
What if somebody talks to me and I can't think of what to say?			
What if they see how scared I am?			
22. My voice leaves me or sounds funny when I am talking to others			
23. I usually do not speak to anyone until they speak to me			
24. When I am with other people, I think "scary" thoughts. Sometimes I think			
If I goof up, I will really feel bad			
What are they thinking of me?			
Whatever I say will sound stupid			
25. Before going someplace, I feel :			
Sweaty			
Like I have to go to the bathroom			
My heart beats fast			
I get a headache or stomachache			

My stomach feels funny			
26. When I am in a social situation, I feel:			
Sweaty			
I shake			
I fee like I have to go to the bathroom			
My heart beats fast			
I have a headache or stomach ache			

CDI

Kids sometimes have different feelings and ideas.

This form lists the feelings and ideas in groups. From each group of three sentences, pick one sentence that describes you best for the past two weeks. After you pick a sentence from the first group, go onto the next group.

There is no right or wrong answer. Just pick the sentence that best describes the way you have been recently. Put a mark/tick next to your answer. Put the mark next to the sentence that you pick.

Item 1
I am sad once in a while
I am sad many times
I am sad all the time

Item 2
Nothing will ever work out for me
I am not sure if things will work out for me
Things will work out for me O.K

Item 3
I do most things O.K.
I do many things wrong
I do everything wrong

Item 4
I have fun in many things
I have fun in some things
Nothing is fun at all

Item 5
I am bad all the time
I am bad many times
I am bad once in a while

Item 6
I think about bad things happening to me once in a while
I worry that bad things will happen to me
I am sure that terrible things will happen to me

Item 7
I hate myself
I do not like myself
I like myself

Item 8
All bad things are my fault
Many bad things are my fault
Bad things are not usually my fault

Item 9
I do not think about killing myself
I think about killing myself but I would not do it
I want to kill myself

Item 10
I feel like crying every day
I feel like crying many days
I feel like crying once in a while

Item 11
Things bother me all the time
Things bother me many times
Things bother me once in a while

Item 12
I like being with people
I do not like being with people many times
I do not want to be with people at all

Item 13

I cannot make up my mind about things

It is hard to make up my mind about things

I make up my mind about things easily

Item 14

I look O.K.

There are some bad things about my looks

I look ugly

Item 15

I have to push myself all the time to do my schoolwork

I have to push myself many times to do my school work

Doing schoolwork is not a big problem

Item 16

I have trouble sleeping every night

I have trouble sleeping many nights

I sleep pretty well

Item 17

I am tired once in a while

I am tired many days

I am tired all the time

Item 18

Most days I do not feel like eating

Many days I do not feel like eating

I eat pretty well

Item 19

I do not worry about aches and pains

I worry about aches and pains many times

I worry about aches and pains all the time

Item 20

I do not feel alone

I feel alone many times

I feel alone all the time

Item 21

I never have fun at school

I have fun at school only once in a while

I have fun at school many times

Item 22

I have plenty of friends

I have some friends but I wish I had more

I do not have any friends

Item 23

My schoolwork is alright

My schoolwork is not as good as before

I do very badly in subjects I used to be good in

Item 24

I can never be as good as other kids

I can be as good as other kids if I want to

I am just as good as other kids

Item 25

Nobody really loves me

I am not sure if anybody loves me

I am sure that somebody loves me

Item 26

I usually do what I am told

I do not do what I am told most times

I never do what I am told

Item 27

I get along with people

I get into fights many times

I get into fights all the time

EMBU-c

Please complete this questionnaire, where possible for both of your parents. Put a number in the box, using the scale below:

1 = no, never 2 = yes, but seldom 3 = yes, often 4 = yes, most of the time	Mother	Father
When you come home, you have to tell your parents what you have been doing		
Your parents want you to reveal your secrets to them.		
Your parents want to decide how you should be dressed or how you should look		
Your parents tell you what you should do after school hours		
Your parents know exactly what you are allowed to do and what not		
Your parents allow you to decide what you want to do.		
Your parents take care that you behave by the rules.		
Your parents watch you very carefully		
Your parents think that they have to decide everything for you		
Your parents keep a check on you.		
When you are unhappy, your parents console you and cheer you up.		
Your parents like you just the way you are.		
Your parents play with you and are interested in your hobbies.		
Your parents listen to you and consider your opinion.		
Your parents want to be with you.		
Your parents show that they love you		
Your parents and you like each other.		
When you have done something stupid, you can make it up with your parents		
Your parents give you compliments.		
Your parents help you when you have to do something difficult		
Your parents tell you that they don't like your behaviour at home.		
Your parents treat you unfairly		
Your parents wish that you were like somebody else		
You are blamed for everything that goes wrong		
Your parents punish you for no reason		
Your parents criticize you in front of others		

You feel disappointed because your parents don't give you what you want.		
Your parents are mean and grudging towards you.		
If something happens at home, you are the one who gets blamed for it		
Your parents beat you for no reason.		
Your parents worry about what you are doing after school		
Your parents are afraid that something might happen to you		
Your parents worry about you getting into trouble.		
Your parents worry about you doing dangerous things.		
Your parents worry about you making a mistake.		
Your parents are afraid when you do something on your own		
Your parents are anxious people and therefore you are not allowed to do as many things as other children		
Your parents warn you of all possible dangers		
Your parents are worried when they don't know what you are doing		
Your parents want to keep you from all possible dangers		

Appendix 9: ANCOVAs controlling for anxiety and depression

Questionnaire subscales	Depression (CDI)	Anxiety (STAI)
Chalder Fatigue Questionnaire	F(2,186) = 114.302, p = .000	F(2,187) = 148.738, p = .000
Work and Social Adjustment Questionnaire	F(2,186) = 248.025, p = .000	F(2,187) = 324.395, p = .000
S.F.36 Physical Functioning Scale	F(186) = 45.859, p = .000	F(2,187) = 74.381, p = .000
Insomnia Scale	F(2,187) = 10.215, p = .000	F(2,187) = 35.536, p = .000
State Trait Anxiety Inventory for children	F(2,185) = .281, p = .755**	
Children's Depression Inventory Total Score		F(2,185) = 19.952, p = .000
Eysenck Personality Questionnaire – Neuroticism	F(2,186) = 2.634, p = .074**	F(2,187) = 3.506, p = .032
Eysenck Personality Questionniare – Extraversion	F(2,185) = 4.635, p = .011	F(2,187) = 4.126, p = .018
Social Desirability Scale	F(2,185) = 11.698, p = .000	F(2,186) = 9.480, p = .000
Pediatric Quality of Life Scale (overall)	F(2,185) = 98.265, p = .000	F(2,185) = 141.281, p = .000
Cognitive Behavioural Responses Questionnaire –Fear Avoidance	F(1,109) = 30.865, p = .000	F(1,110) = 43.011, p = .000
Cognitive Behavioural Responses Questionnaire –Catastrophising	F(1,108) = 29.096, p = .000	F(1,109) = 42.394, p = .000
Cognitive Behavioural Responses Questionnaire –Damage	F(1,109) = 8.346, p = .005	F(1,110) = 12.890, p = .000

Cognitive Behavioural Responses Questionnaire –Embarrassment Avoidance	F(1,108) = 3.023, p = .085**	F(1,109) = 6.086, p = .015
Cognitive Behavioural Responses Questionnaire –Symptom Focusing	F(1,108) = 5.981, p = .016	F(1,109) = 11.238, p = .001
Cognitive Behavioural Responses Questionnaire –All or nothing Behaviour	F(1,109) = 29.128, p = .000	F(1,110) = 35.466, p = .000
Cognitive Behavioural Responses Questionnaire –Avoidance Behaviour	F(1,109) = 37.963, p = .000	F(1,110) = 50.974, p = .000
** denotes scales that are no longer significantly different between groups when controlling for anxiety / depression		

Appendix 10: Self-report questionnaires – mother

CHRONIC FATIGUE SYNDROME

QUESTIONNAIRE PACK FOR PARENTS OF ADOLESCENTS WITH CFS

Thank you for agreeing to participate in this study. We are very interested in finding out more about your daughter's illness and the impact the symptoms have had on your lives.

This booklet contains a number of questions about the nature of your daughter's symptoms, how he manages these symptoms and the impact these have had on his physical health and psychological well-being

There are no right or wrong answers to these questions. We are most interested in your own personal views.

We ask you to answer the questions as honestly and as quickly as possible.

We are interested in both your perceptions of your child's health, and your own health.

This is to be filled in independently of your daughter. We would be very grateful if you completed these questionnaires without discussing it with your daughter.

This questionnaire is completely

CONFIDENTIAL.

Thank you very much for your time

Demographic and personal data

Ethnicity (please tick the appropriate box)

White Caucasian	Black	Asian	Other	Please specify
☐	☐	☐	☐	……

Please indicate your occupational status

Employed	☐
Unemployed	☐
Student	☐
Housewife/husband	☐
Disabled/on disability allowance	☐
Other:	☐

If employed, what is your occupation?

……

If unemployed, what was your most recent occupation?

……..

Please indicate the occupational status of your partner.

Employed	☐
Unemployed	☐
Student	☐
Househusband/wife	☐
Disabled/on disability allowance	☐
Other:	☐

What is your marital status?

Married	☐
Single	☐
Divorced	☐
Co-habitant	☐
Widow(er)	☐
Partner, but not living together	☐
Other:	☐
Please specify	……..

Please tick whether you have had a past-history of illness or problems related to fatigue, or indeed are currently suffering from such problems.

Illness/Problem	Past-history	Currently Suffering
C.F.S.	☐	☐
Depression	☐	☐
Anxiety	☐	☐
Alcohol-related problem	☐	☐
Drugs-related problem	☐	☐
Any other psychiatric problem?		
- ADHD	☐	☐
- Asperger's	☐	☐

What is your relationship to the patient?

- Birth Mother ☐
- Birth Father ☐
- Step-mother ☐
- Step-father ☐
- Adoptive Mother ☐
- Adoptive Father ☐

C.B.R.Q.

Please indicate how much you agree or disagree with the following statements about your daughter's current symptoms by ticking the appropriate box.

VIEWS ABOUT YOUR DAUGHTHER'S SYMPTOMS	STRONGLY DISAGREE	DISAGREE	NEITHER AGREE NOR DISAGREE	AGREE	STRONGLY AGREE
I am afraid that my daughter will make her symptoms worse if she exercises	☐	☐	☐	☐	☐
Her symptoms would be relieved if she were to exercise	☐	☐	☐	☐	☐
Avoiding unnecessary activities is the safest thing my daughter can do to prevent the symptoms from worsening	☐	☐	☐	☐	☐
The severity of my daughter's symptoms must mean there is something serious going on in her body	☐	☐	☐	☐	☐
Even though my daughter experiences symptoms, I don't think they are actually harming her	☐	☐	☐	☐	☐
When my daughter experiences symptoms, her body is telling her that there is something seriously wrong.	☐	☐	☐	☐	☐

Physical activity makes my daughter's symptoms worse	☐	☐	☐	☐	☐
Doing less helps my daughter's symptoms	☐	☐	☐	☐	☐
Symptoms are a signal that my daughter is damaging herself	☐	☐	☐	☐	☐
I am afraid my daughter will have more symptoms if she is not careful	☐	☐	☐	☐	☐
My daughter should avoid exercise when she has symptoms	☐	☐	☐	☐	☐
I worry that my daughter may become permanently bedridden because of her symptoms	☐	☐	☐	☐	☐

I think that if my daughter's symptoms get too severe they may never decrease	☐	☐	☐	☐	☐
My daughter's illness is awful and I feel that it overwhelms her	☐	☐	☐	☐	☐
My daughter will never feel right again	☐	☐	☐	☐	☐

We are interested in how your daughter responds to or manages her symptoms at the moment. Listed below are a number of different responses that people may have to their symptoms.

Please indicate how often your daughter responds in the following ways by ticking the appropriate box. Choose the most accurate answer for YOUR DAUGHTER, not what you think "most people" would say or do.

MANAGING SYMPTOMS	Never	Some-times	Quite often	Very Often	All the time
My daughter stays in bed to control her symptoms	☐	☐	☐	☐	☐
When my daughter experiences symptoms, she rests.	☐	☐	☐	☐	☐
My daughter tends to avoid activities that make her symptoms worse	☐	☐	☐	☐	☐
My daughter tends to nap during the day to control her symptoms	☐	☐	☐	☐	☐
My daughter tends to overdo things when she feels energetic	☐	☐	☐	☐	☐
My daughter finds herself rushing to get things done before she crashes	☐	☐	☐	☐	☐
My daughter tends to overdo things and then rest up for a while	☐	☐	☐	☐	☐
My daughter tends to do a lot on a good day and rest on a bad day	☐	☐	☐	☐	☐
My daughter sleeps when she's tired in order to control her symptoms	☐	☐	☐	☐	☐
My daughter avoids making social arrangements in case she is not up to it	☐	☐	☐	☐	☐
My daughter avoids exerting herself in order to control her symptoms	☐	☐	☐	☐	☐
My daughter is a bit all or nothing when it comes to doing things	☐	☐	☐	☐	☐
My daughter avoids stressful situations	☐	☐	☐	☐	☐

Which of the following best describes the causes of your daughter's symptoms (please tick as many boxes as apply):

Environment	☐	Stress	☐
Problems at school	☐	Family problems	☐
Problems with friends	☐	Virus	☐
Not enough exercise	☐	Too much exercise	☐

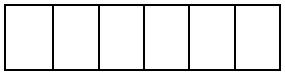
Describing your family (02.03.2015)

We would like you to tell us about how you see your family at the moment. So we are asking for YOUR view of your family.

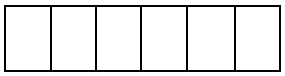
When people say 'your family' they often mean the people who live in your house. But we want you to choose who you want to count as the family you are going to describe.

All the questions are answered the same way: you put a tick □ in the box which best matches how you see your family. So if a statement was:

"Our family wants to stay together" and you really feel this fits you completely, you would put a tick in box 1 on that line for "extremely well".



If a statement was "We are always fighting each other" and you felt this was not especially true of your family, you would put a tick in box 5 for "not well".



For each item, make your choice by putting □ in just one of the boxes numbered 1 to 6. Do not think for too long about any question, it is how they all add up that we will be interested in, rather than any specific answers. But do try to tick one of the boxes for each question.

For each line, would you say:

1. That describes our family: Extremely well
2. That describes our family: Very well
3. That describes our family: Well
4. That describes our family: A bit
5. That describes our family: Not well
6. That describes our family: Not at all

	1. Extremely well	2. Very well	3. Well	4. A bit	5. Not well	6. Not at all
Being in this family is important to us	☐	☐	☐	☐	☐	☐
People do things that show that they care about each other in my family	☐	☐	☐	☐	☐	☐
We are a very organised family	☐	☐	☐	☐	☐	☐
It feels risky to disagree in our family	☐	☐	☐	☐	☐	☐
People in my family interfere too much in each other's lives	☐	☐	☐	☐	☐	☐
Our family shares enjoyable times together	☐	☐	☐	☐	☐	☐
One person tends to get blamed for everything in my family	☐	☐	☐	☐	☐	☐
People often don't tell each other the truth in my family	☐	☐	☐	☐	☐	☐
If something is going wrong in our family we know we can change it	☐	☐	☐	☐	☐	☐
The rules are fair in our family	☐	☐	☐	☐	☐	☐
We find it hard to deal with everyday problems	☐	☐	☐	☐	☐	☐
When people in my family get angry they ignore each other on purpose	☐	☐	☐	☐	☐	☐
Life in our family is very difficult.	☐	☐	☐	☐	☐	☐
Each of us gets listened to in our family	☐	☐	☐	☐	☐	☐
People in my family are willing to change their views about things	☐	☐	☐	☐	☐	☐
There are no rules in my family	☐	☐	☐	☐	☐	☐
In our family it is OK to show how you feel	☐	☐	☐	☐	☐	☐
In my family people prefer to watch TV than to spend time with each other	☐	☐	☐	☐	☐	☐
Other people look down on my family because we are different	☐	☐	☐	☐	☐	☐
When one of us is upset they get looked after within the family	☐	☐	☐	☐	☐	☐

For each line, would you say:

1. That describes our family: Extremely well
2. That describes our family: Very well
3. That describes our family: Well
4. That describes our family: A bit
5. That describes our family: Not well
6. That describes our family: Not at all

	1. Extremely well	2. Very well	3. Well	4. A bit	5. Not well	6. Not at all
Respecting elders is important in our family	☐	☐	☐	☐	☐	☐
It feels miserable in our family	☐	☐	☐	☐	☐	☐
Being with some family members can be frightening	☐	☐	☐	☐	☐	☐
People in our family lie to each other	☐	☐	☐	☐	☐	☐
In my family we blame each other when things go wrong	☐	☐	☐	☐	☐	☐
Things always seem to go wrong for my family	☐	☐	☐	☐	☐	☐
We hardly ever put each other down in my family	☐	☐	☐	☐	☐	☐
People hit each other a lot in my family	☐	☐	☐	☐	☐	☐
In my family we ignore our problems in the hope that they will go away	☐	☐	☐	☐	☐	☐
In my family we talk to each other about the things that matter to us	☐	☐	☐	☐	☐	☐
We are good at finding new ways to deal with things that are difficult	☐	☐	☐	☐	☐	☐
People in the family are nasty to each other	☐	☐	☐	☐	☐	☐
We trust each other	☐	☐	☐	☐	☐	☐
We get into a muddle about who should do what	☐	☐	☐	☐	☐	☐
In my family it's OK to spend time on your own if you want to	☐	☐	☐	☐	☐	☐
People slam doors, throw things or make a lot of noise if they are upset	☐	☐	☐	☐	☐	☐
My family feels part of a wider community	☐	☐	☐	☐	☐	☐
We seem to go from one crisis to another in my family	☐	☐	☐	☐	☐	☐
My family is very strict	☐	☐	☐	☐	☐	☐
We feel hopeful about the future	☐	☐	☐	☐	☐	☐

C.F.Q. We would like to know whether or not YOU have been having any problems with feeling tired, weak or lacking in energy in the last few weeks. Please answer ALL the questions simply by ticking the answer which you think most applies to YOU. We would like to know how you feel either at the moment or recently, rather than a long time ago. If you have been feeling tired for a long time, we want you to compare yourself to how you felt when last well.

Do you have problems with tiredness? ☐	Less than usual ☐	No more than usual ☐	More than usual ☐	Much more than usual ☐
Do you need to rest more? ☐	Less than usual ☐	No more than usual ☐	More than usual ☐	Much more than usual ☐
Do you feel sleepy or drowsy? ☐	Less than usual ☐	No more than usual ☐	More than usual ☐	Much more than usual ☐
Do you have problems starting things? ☐	Less than usual ☐	No more than usual ☐	More than usual ☐	Much more than usual ☐
Do you lack energy? ☐	Better than usual ☐	No more than usual ☐	More than usual ☐	Much more than usual ☐
Do you have less strength in your muscles? ☐	Better than usual ☐	No more than usual ☐	More than usual ☐	Much more than usual ☐
Do you feel weak? ☐	Less than usual ☐	Same as usual ☐	More than usual ☐	Much more than usual ☐
Do you have difficulty concentrating? ☐	Less than usual ☐	Same as usual ☐	More than usual ☐	Much more than usual ☐
Do you make slips of the tongue when speaking? ☐	Less than usual ☐	No more than usual ☐	More than usual ☐	Much more than usual ☐
Do you find it more difficult to find the correct word? ☐	Less than usual ☐	No more than usual ☐	More than usual ☐	Much more than usual ☐

How is your memory?	Better than usual	No worse than usual	Worse than usual	Much worse than usual
	☐	☐	☐	☐

The next questions ask about muscle pain:

Do your muscles hurt at rest?	Less than usual	No more than usual	Worse than usual	Much worse than usual
	☐	☐	☐	☐

Do your muscles hurt after exercise?	Less than usual	No more than usual	Worse than usual	Much worse than usual
	☐	☐	☐	☐

Y.S.I.

Listed below are statements that a person might use to describe himself or herself. Please read each statement and decide how well it describes you. When you are not sure, base your answer on what you emotionally feel, not on what you think to be true. Then choose the highest rating from 1 to 6 that describes you and write the number in the space after the statement.

RATING SCALE:1 = Completely untrue of me

2 = Mostly untrue of me

3 = Slightly more true than untrue

4 = Moderately true of me

5 = Mostly true of me

6 = Describes me perfectly

I put others' needs before my own, or else I feel guilty.

I feel guilty when I let other people down or disappoint them.

I give more to other people than I get back in return.

I'm the one who usually ends up taking care of the people I'm close to.

There is almost nothing I couldn't put up with if I loved someone.

I am a good person because I think of others more than of myself.

At work, I'm usually the one to volunteer to do extra tasks or to put in extra time.

No matter how busy I am, I can always find time for others.

I can get by on very little, because my needs are minimal.

I'm only happy when those around me are happy.

I'm so busy doing for the people that I care about, that I have little time for myself.

I've always been the one who listens to everyone else's problems.

I'm more comfortable giving a present than receiving one.

Other people see me as doing too much for others and not enough for myself.

No matter how much I give, it is never enough.

If I do what I want, I feel very uncomfortable.

It's very difficult for me to ask others to take care of my needs.

BES

Please read each statement below and decide how well it describes how you have felt over the past six months. Please indicate your answer by placing a tick under the column that best describes what you think. To decide whether a given answer has been typical of your way of looking at things over the past six months, simply keep in mind what you are like most of the time.

	Totally agree	Agree very much	agree slightly	Neutral	Disagree slightly	Disagree very much	Totally disagree
It is a sign of weakness if I have miserable thoughts.	☐	☐	☐	☐	☐	☐	☐
If I have difficulties I should not admit them to others.	☐	☐	☐	☐	☐	☐	☐
If I lose control of my emotions in front of others, they will think less of me.	☐	☐	☐	☐	☐	☐	☐
I should be able to control my emotions.	☐	☐	☐	☐	☐	☐	☐
If I am having difficulties it is important to put on a brave face.	☐	☐	☐	☐	☐	☐	☐
If I show signs of weakness then others will reject me.	☐	☐	☐	☐	☐	☐	☐
I should not let myself give in to negative feelings.	☐	☐	☐	☐	☐	☐	☐
I should be able to cope with difficulties on my own without turning to others for support.	☐	☐	☐	☐	☐	☐	☐
To be acceptable to others, I must keep any difficulties or negative feelings to myself.	☐	☐	☐	☐	☐	☐	☐

It is stupid to have miserable thoughts.	☐	☐	☐	☐	☐	☐	☐
It would be a sign of weakness to show my emotions in public.	☐	☐	☐	☐	☐	☐	☐
Others expect me to always be in control of my emotions.	☐	☐	☐	☐	☐	☐	☐

P.S. Please circle the number that best corresponds to your agreement with each statement below.

	Strongly disagree				Strongly agree
1. My parents set very high standards for me	1	2	3	4	5
2. Organisation is very important to me.	1	2	3	4	5
3. As a child, I was punished for doing things less than perfectly.	1	2	3	4	5
4. If I do not set the highest standards for myself, I am likely to end up a second-rate person.	1	2	3	4	5
5. My parents never tried to understand my mistakes.	1	2	3	4	5
6. It is important to me that I be thoroughly competent in everything I do.	1	2	3	4	5
7. I am a neat person.	1	2	3	4	5
8. I try to be an organised person.	1	2	3	4	5
9. If I fail at work, I am a failure as a person.	1	2	3	4	5
10. I should be upset if I make a mistake.	1	2	3	4	5
11. My parents wanted me to be the best at everything.	1	2	3	4	5
12. I set higher goals than most people.	1	2	3	4	5
13. If someone does a task at work better than I, then I feel like I failed the whole task.	1	2	3	4	5
14. If I fail partly, it is as bad as being a complete failure.	1	2	3	4	5
15. Only outstanding performance is good enough in my family.	1	2	3	4	5
16. I am very good at focusing my efforts on attaining a goal.	1	2	3	4	5
17. Even when I do something very carefully, I often feel that it is not quite right.	1	2	3	4	5
18. I hate being less than best at things	1	2	3	4	5
19. I have extremely high goals.	1	2	3	4	5

20. My parents have expected excellence from me.	1	2	3	4	5
21. People will probably think less of me if I make a mistake	1	2	3	4	5
22. I never felt like I could meet my parents' expectations.	1	2	3	4	5
23. If I do not do as well as other people, it means I am an inferior human being.	1	2	3	4	5
24. Other people seem to accept lower standards from themselves than I do.	1	2	3	4	5
25. If I do not do well all the time, people will not respect me.	1	2	3	4	5
26. My parents have always had higher expectations for my future than I have.	1	2	3	4	5
27. I try to be a neat person.	1	2	3	4	5
28. I usually have doubts about the simple everyday things I do.	1	2	3	4	5
29. Neatness is very important to me.	1	2	3	4	5
30. I expect higher performance in my daily tasks than most people.	1	2	3	4	5
31. I am an organised person.	1	2	3	4	5
32. I tend to get behind in my work because I repeat things over and over.	1	2	3	4	5
33. It takes me a long time to do something 'right'.	1	2	3	4	5
34. The fewer mistakes I make, the more people will like me.	1	2	3	4	5
35. I never felt like I could meet my parents' standards.	1	2	3	4	5

EPQ-R (Short Form)

Please answer ALL of the questions, TICKING the answer you feel best describes you. Answer the questions honestly and do not spend too much time thinking about them. PLEASE BE SURE TO ANSWER ALL QUESTIONS.

1. Does your mood often go up and down?.....YES ☐NO ☐

2. Are you a talkative person?.....YES ☐NO ☐

3. Do you ever feel 'just miserable' for no reason?.....YES☐NO ☐

4. Are you rather lively?.....YES ☐NO ☐

5. Are you an irritable person?.....YES ☐NO ☐

6. Do you enjoy meeting new people?.....YES☐NO ☐

7. Are your feelings easily hurt?.....YES ☐NO ☐

8. Can you usually let yourself go and enjoy yourself at a lively party?
YES☐NO☐

9. Do you often feel 'fed-up'?.....YES ☐NO ☐

10. o you usually take initiative in making new friends?.....YES ☐NO ☐

11. Would you call yourself a nervous person?.....YES ☐NO ☐

12. Can you easily get some life into a rather dull party?.....YES ☐NO ☐

13. Are you a worrier?.....YES ☐NO ☐

14. Do you tend to keep in the background on social occasions?..YES ☐NO ☐

15 Would you call yourself tense or 'highly-strung'?.....YES ☐NO ☐

16 Do you like mixing with people?.....YES ☐NO ☐

17 Do you worry too long after an embarrassing experience?.....YES☐NO ☐

18 Do you like plenty of bustle and excitement around you?.....YES☐NO ☐

19 Do you suffer from 'nerves'?.....YES ☐NO ☐

20 Are you mostly quiet when you are with other people?.....YES ☐ NO ☐

21Do you often feel lonely?.....YES ☐NO ☐

22 Do other people think of you as being very lively?.....YES ☐NO ☐

23 Are you often troubled about feelings of guilt?.....YES ☐NO ☐

24 Can you get a party going?.....YES☐NO ☐

G.H.Q. We would like to know how your health has been in general over the past few weeks. Please answer ALL the questions simply by TICKING the answer you think best applies to you. Remember that we want to know about present and recent health. HAVE YOU RECENTLY;

been able to concentrate on whatever you're doing	Better than usual ☐	Same as Usual ☐	Less than usual ☐	Much less than usual ☐
lost much sleep due to worry	Not at all ☐	No more than usual ☐	More than usual ☐	Much more than usual ☐
felt that you are playing a useful part in things	More so than usual ☐	Same as usual ☐	Less useful than usual ☐	Much less useful ☐
felt capable of making decisions about things	More so than usual ☐	Same as usual ☐	Less useful than usual ☐	Much less capable ☐
felt constantly under strain	Not at all ☐	No more than usual ☐	Rather more than usual ☐	Much more than usual ☐
felt you could not overcome your difficulties	Not at all ☐	No more than usual ☐	Rather more than usual ☐	Much more than usual ☐
been able to enjoy your normal day-to-day activities	More so than usual ☐	Same as usual ☐	Less so than usual ☐	Much less than usual ☐
been able to face up to your problems	More so than usual ☐	Same as usual ☐	Less so than usual ☐	Much less than usual ☐
been feeling unhappy and depressed	Not at all ☐	No more than usual ☐	Rather more than usual ☐	Much more than usual ☐
been losing confidence in yourself	Not at all ☐	No more than usual ☐	Rather more than usual ☐	Much more than usual ☐
been thinking of yourself as a worthless person	Not at all ☐	No more than usual ☐	Rather more than usual ☐	Much more than usual ☐
been feeling reasonably happy, all things considered	More so than usual ☐	About the same as usual ☐	Less so than usual ☐	Much less than usual ☐

FRQ Instructions: When a person suffers from an illness for a long time, it is likely to affect his/her family. There are a number of different ways in which family members cope with the problems of a person's illness. This form is designed to assess those ways of coping. On the following pages, there is a series of questions about your feelings and reactions to the person in your family who is ill. We have called the ill person ''X.'' Please read the questions and mark the reply which comes closest to describing how you have felt or acted over the past 3 months.

Please remember that we are trying to find out how things have really been, rather than how you would like them to have been, and so we would like you to be as honest as possible. There are no right or wrong answers. Please remember that your replies are given in the strictest confidence.

	Never	Rarely	Occasionally	Often	Very Often
Thought about how X must be feeling?					
Worried about X's illness?					
Tried to work out what you would do in X's position?					
Felt that X's illness has drawn you together?					
Reminded X to slow down?					
Made allowances for X when he/she has been irritable or unreasonable?					
Insisted that X rest?					
Tried to find out more about X's illness by reading, talking to others etc.					
Tried to cheer X up e.g., by bringing treats or presents or arranging entertainment?					
Protected X from seeing other people?					
Spent time discussing X's illness with him or her?					
Encouraged X to get support from other people?					

Felt that there is nothing really wrong with X?					
Wished that you could get some of the attention that X gets?					
Felt that X has used his/her illness to get you to do things you did not really want to do?					
Felt that X may be exaggerating his/her symptoms?					
Been angry with X because he/she cannot do what he/she used to do?					
Felt that X is using his/her illness to avoid doing things he/she usually does?					
Thought that X should make more of an effort to do things?					
Felt frustrated about the practical limitations that X's illness has on your life?					
Felt that your own health might be suffering because of X's illness?					
Felt let down by X?					
Felt that attending to X's illness has caused you to neglect the needs of other family members?					
Felt that you could not cope any longer with X's illness?					
Felt that X does not understand the impact that his/her illness has had on your life?					

Adolescent APQ	Definitely agree	Slightly agree	Slightly disagree	Definitely disagree
1. S/he prefers to do things with others rather than on her/his own.				
2. S/he prefers to do things the same way over and over again.				
3. If s/he tries to imagine something, s/he finds it very easy to create a picture in her/his mind.				
4. S/he frequently gets so strongly absorbed in one thing that s/he loses sight of other things.				
5. S/he often notices small sounds when others do not.				
6. S/he usually notices car number plates or similar strings of information.				
7. Other people frequently tell her/him that what s/he has said is impolite, even though s/he thinks it is polite.				
8. When s/he is reading a story, s/he can easily imagine what the characters might look like.				
9. S/he is fascinated by dates.				
10. In a social group, s/he can easily keep track of several different people's conversations.				
11. S/he finds social situations easy.				
12. S/he tends to notice details that others do not.				
13. S/he would rather go to a library than a party.				
14. S/he finds making up stories easy.				
15. S/he finds her/himself drawn more strongly to people than to things.				
16. S/he tends to have very strong interests, which s/he gets upset about if s/he can't pursue.				
17. S/he enjoys social chit-chat.				
18. When s/he talks, it isn't always easy for				

others to get a word in edgeways.				
19. S/he is fascinated by numbers.				
20. When s/he is reading a story, s/he finds it difficult to work out the characters' intentions.				
21. S/he doesn't particularly enjoy reading fiction.				
22. S/he finds it hard to make new friends.				
23. S/he notices patterns in things all the time.				
24. S/he would rather go to the theatre than a museum.				
25. It does not upset him/her if his/her daily routine is disturbed.				
26. S/he frequently finds that s/he doesn't know how to keep a conversation going.				
27. S/he finds it easy to ''read between the lines'' when someone is talking to her/him.				
28. S/he usually concentrates more on the whole picture, rather than the small details.				
29. S/he is not very good at remembering phone numbers.				
30. S/he doesn't usually notice small changes in a situation, or a person's appearance.				
31. S/he knows how to tell if someone listening to him/her is getting bored.				
32. S/he finds it easy to do more than one thing at once.				
33. When s/he talks on the phone, s/he is not sure when it's her/his turn to speak.				
34. S/he enjoys doing things spontaneously.				
35. S/he is often the last to understand the point of a joke.				
36. S/he finds it easy to work out what someone is thinking or feeling just by looking at their face.				
37. If there is an interruption, s/he can switch back to what s/he was doing very				

quickly.				
38. S/he is good at social chit-chat.				
39. People often tell her/him that s/he keeps going on and on about the same thing.				
40. When s/he was younger, s/he used to enjoy playing games involving pretending with other children.				
41. S/he likes to collect information about categories of things (e.g. types of car, types of bird, types of train, types of plant, etc.).				
42. S/he finds it difficult to imagine what it would be like to be someone else.				
43. S/he likes to plan any activities s/he participates in carefully.				
44. S/he enjoys social occasions.				
45. S/he finds it difficult to work out people's intentions.				
46. New situations make him/her anxious.				
47. S/he enjoys meeting new people.				
48. S/he is a good diplomat.				
49. S/he is not very good at remembering people's date of birth.				
50. S/he finds it very to easy to play games with children that involve pretending.				

HAD SCALE

I feel tense or "wound up"

Most of the time

A lot of the time

Occasionally

Not at all

I feel as if I have slowed down

Nearly all the time

Very often

Sometimes

Not at all

I still enjoy the things I used to do

Definitely as much

Not quite so much

Only a little

Hardly at all

I get a sort of frightened feeling like "butterflies" in the stomach

Not at all

Occasionally

Quite often

Very often

I get a sort of frightened feeling as if something awful is about to happen

Very definitely & quite badly

Yes but not too badly

A little but it doesn't worry me

Not at all

I have lost interest in my appearance

Definitely

I don't take so much care as I should

I may not take quite as much care

I take just as much care as ever

I can laugh and see the funny side of things

As much as I always could

Not quite as much now

Definitely not quite so much now

Not at all

I feel restless as if I have to be on the move

Very much indeed

Quite a lot

Not very much

Not at all

Worrying thoughts go through my mind

A great deal of the time

A lot of the time

From time to time but not often

Only occasionally

I look forward with enjoyment to things

As much as I ever did

Rather less than I used to

Definitely less than I used to

Hardly at all

I feel cheerful

Not at all

Not often

Sometimes

Most of the time

I get sudden feelings of panic

Very often indeed

Quite often

Not very often

Not at all

I can sit at ease and feel relaxed

Definitely

Usually

Not often

Not at all

I can enjoy a good book or radio or TV programme

Often

Sometimes

Not often

Very seldom

My appetite is

Very poor

Fairly poor

Quite good

Very good

I'm awake before I need to get up.

For two hours or more

For about an hour

For less than an hour

Not at all, I sleep until it is time to get up

ASQ

Instructions: We are interested in how you experience and manage your emotions. Obviously, different situations bring out somewhat different responses, but think about what you usually do. Please try to respond to each item separately in your mind from each other item. Do not indicate agreement with things that you think you should do or wish you do. Instead, choose your answers thoughtfully, and make your answers about what is true FOR YOU. Please answer every item. There are no "right" or "wrong" answers, so choose the most accurate answer for YOU−—not what you think "most people" would say or do. Use the scale below to answer each item

1----------2----------3----------4----------5

not true of me at all — a little bit — moderately — quite a bit — extremely true of me

1. People usually can't tell how I am feeling inside. 1—2—3—4—5

2. I have my emotions well under control 1—2—3—4—5

3. I can tolerate having strong emotions. 1—2—3—4—5

4. I can avoid getting upset by taking a different perspective on things. 1-2-3-4-5

5. I often suppress my emotional reactions to things. 1—2—3—4—5

6. It's ok if people see me being upset. 1—2—3—4—5

7. I can calm down very quickly 1—2—3—4—5

8. I am able to let go of my feelings. 1—2—3—4—5

9. I am good at hiding my feelings. 1—2—3—4—5

10. People usually can't tell when I am upset. 1—2—3—4—5

11. It's ok to feel negative emotions at times. 1—2—3—4—5

12. I can get out of a bad mood very quickly. 1—2—3—4—5

13. People usually can't tell when I am sad. 1—2—3—4—5

14. I can tolerate being upset. 1—2—3—4—5

15. I can act in a way that people don't see me being upset. 1—2—3—4—5

16. I know exactly what to do to get myself into a better mood. 1—2—3—4—5

17. There is nothing wrong with feeling very emotional. 1—2—3—4—5

18. I could easily fake emotions. 1—2—3—4—5

19. I can get into a better mood quite easily. 1—2—3—4—5

20. I can hide my anger well if I have to. 1—2—3—4—5

F.Q.

Choose a number from the scale below to show how much you would avoid each of the situations listed below because of fear or other unpleasant feelings. Then write the number you choose in the box opposite each situation.

0	1	2	3	4	5	6	7	8
Would not avoid		Slightly avoid		Definitely avoid		Markedly avoid		Always avoid

Injections or minor surgery	
Eating or drinking with other people	
Hospitals	
Travelling alone by bus or coach	
Walking alone in busy streets	
Being watched or stared at	
Going into crowded shops	
Talking to people in authority	
Sight of blood	
Being criticised	
Going alone far from home	
Thought of injury or illness	
Speaking or acting to an audience	
Large open spaces	
Going to the dentist	
Other situations (describe)	

Now choose a number from the scale below to show how much you are troubled by each problem listed, and write the number in the box opposite.

0 1 2	3 4 5	6 7	8
Slightly troublesome	Definitely troublesome	Markedly troublesome	Very severely troublesome

Feeling miserable or depressed	
Feeling irritable or angry	
Feeling tense or panicky	
Upsetting thoughts coming into your mind	
Feeling you or your surrounding are strange or unreal	
Other feelings (describe)	

WHO

Please indicate for each of the five statements which is closest to how you have been feeling over the last two weeks.

Notice that higher numbers mean better well-being.

Example: If you have felt cheerful and in good spirits more than half of the time during the last two weeks, put a tick in the box with the number 3 in the upper left corner.

	All of the time	Most of the time	More than half of the time	Less than half of the time	Some of the time	At no time
1 I have felt cheerful and in good spirits	5	4	3	2	1	0
2 I have felt calm and relaxed	5	4	3	2	1	0
3 I have felt active and vigorous	5	4	3	2	1	0
4 I woke up feeling fresh and rested	5	4	3	2	1	0
5 My daily life has been filled with things that interest me	5	4	3	2	1	0

In the past ONE month, how much of a problem has your child had with…

PHYSICAL FUNCTIONING	Never	Almost never	Some-times	Often	Almost always
1. Walking more than one block	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in sports activities or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Taking a bath or shower by him or herself	0	1	2	3	4
6. Doing chores around the house	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

EMOTIONAL FUNCTIONING	Never	Almost never	Some-times	Often	Almost always
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying about what will happen to him or her	0	1	2	3	4

SOCIAL FUNCTIONING	Never	Almost never	Some-times	Often	Almost always
1. Getting along with other kids	0	1	2	3	4
2. Other kids do not want to be his or her friend	0	1	2	3	4
3. Getting teased by other children	0	1	2	3	4
4. Not able to do things that other children his or her age can	0	1	2	3	4

do					
5. Keeping up when playing with other kids	0	1	2	3	4

SCHOOL FUNCTIONING	Never	Almost never	Some-times	Often	Almost always
1. Paying attention in class	0	1	2	3	4
2. Forgetting things	0	1	2	3	4
3. Keeping up with school work	0	1	2	3	4
4. Missing school because of not feeling well	0	1	2	3	4
5. Missing school to go to the doctors or hospital	0	1	2	3	4

Appendix 11: Child and parent questionnaire measure correlations

		Chronic Fatigue Syndrome	Asthma	Healthy Control
Self-rating scales	CFQ	Pearson r = .214, p = .054	Pearson r = -.082, p = .665	Pearson r = .131, p = .259
	BES	Pearson r = .092, p = .411	Pearson r = .270, p = .156	Pearson r = .211, p = .069
	Concern over mistakes	Pearson r = .057, p = .615	Pearson r = .159, p = .409	Pearson r = .347, p = .003*
	Personal standards	Pearson r = .169, p = .132	Pearson r = .406, p = .029*	Pearson r = .199, p = .093
	Parental expectations	Pearson r = .192, p = .086	Pearson r = .470, p = .010*	Pearson r = .221, p = .062
	Parental criticism	Pearson r = .112, p = .321	Pearson r = .128, p = .508	Pearson r = .251, p = .033*
	Doubts about actions	Pearson r = .186, p = .097	Pearson r = .075, p = .699	Pearson r = .376, p = .001*
	Organisation	Pearson r = .172, p = .124	Pearson r = .051, p = .794	Pearson r = .079, p = .510
	Total Perfectionism	Pearson r = .147, p = .189	Pearson r = .436, p = .018*	Pearson r = .389, p = .001*
	Neuroticism	Pearson r = .188, p = .091	Pearson r = -.214, p = .266	Pearson r = .008, p = .944
	Extraversion	Pearson r = .138, p = .222	Pearson r = -.187, p = .331	Pearson r = .046, p = .697
	Children's depression inventory & Parent's General health questionnaire	Pearson r = .108, p = .342	Pearson r = -.248, p = .194	Pearson r = .131, p = .260
	Children's depression inventory & Parent's	Pearson r = .147, p = .197	Pearson r = -.286, p = .133	Pearson r = .228, p = .049*

	depression			
	State anxiety and parent anxiety	Pearson r = .124, p = .285	Pearson r = -.265, p = .165	Pearson r = .028, p = .813
	Trait anxiety and parent anxiety	Pearson r = .285, p = .012*	Pearson r = -.017, p = .930	Pearson r = .132, p = .257
	Social phobia inventory and parent anxiety	Pearson r = .054, p = .652	Pearson r = -.321, p = .110	Pearson r = .172, p = .140
Scales all completed about the child in question	Negative beliefs about engaging in activity	Pearson r = .431, p = .000*	Pearson r = .412, p = .024*	###
	Catastrophising	Pearson r = .257, p = .021*	Pearson r = .692, p = .000*	###
	Damage	Pearson r = .295, p = .007*	Pearson r = .474, p = .008*	###
	All or nothing behaviour	Pearson r = .606, p = .000*	Pearson r = .647, p = .000*	###
	Avoidance resting behaviour	Pearson r = .526, p = .000*	Pearson r = .413, p = .023*	###
	Physical functioning (PEDS)	Pearson r = .749, p = .000*	Pearson r = .386, p = .035*	Pearson r = .380, p = .001*
	Emotional functioning (PEDS)	Pearson r = .436, p = .000*	Pearson r = -.015, p = .938	Pearson r = .209, p = .070
	Social functioning (PEDS)	Pearson r = .377, p = .001*	Pearson r = .408, p = .028*	Pearson r = .354, p = .002*
	School functioning (PEDS)	Pearson r = .616, p = .000*	Pearson r = -.118, p = .543	Pearson r = .348, p = .002*
	Overall quality of life	Pearson r = .667, p = .000*	Pearson r = .054, p = .782	Pearson r = .284, p = .013*

Appendix 12: Session procedure – verbatim instructions

Welcome to centre:

Hi……, my name is Kate, and I'm going to be working with you today, as you complete a few short tasks for us. Some of the tasks are short, and some a bit longer. Also, some of the tasks involve you talking, thinking and also a pen and paper task.

It's going to take about 1 1/2hour in total, and you can have a break in between the tasks where necessary. If you feel you need a break, just let me know.

Is there anything you would like to ask?

Ok, are you ready to go and get started?

Letter cancellation task:

Ok, the first thing we're going to do is a pen-and-paper task, where I'll ask you to complete it as quickly as possible. This is a concentration test that examines your ability to pick out targets (letters H) among distractors'. The experimenter then placed the practice form in front of a participant and said, ``Here you see several rows of letters. Your task is to find the letter H and each time you find a letter H (experimenter points to one letter), I want you to cross it out with a pencil like this (experimenter demonstrates a single slash over the letter). Every time you see the letter H, cross it out. I want you to work as quickly and accurately as you can. You should cross all Hs and you should cross no other letters. You start with the first row, work from the left to the right, and when finished, go on to the next row until you are finished." Following these instructions, the participant began the test with the practice form.

Do you have any questions? And are you ready for the test?

`Go!'. The experimenter started a stopwatch and finished timing when the participant finished with the Trial 1 form. The Trial 2 form was administered in exactly the same fashion after allowing the participant a brief rest (~30 s±1min).

I'll point out if I notice you have made a mistake, so that you can immediately correct it.

Social Performance Task:

For this next task, I'd like you to speak for about 3minutes on a topic of your choice. You can have 5minutes now to prepare your speech, and although it is important that you speak for the entire period, you can finish early if you feel you must. Your speech will be tape-recorded for my fellow colleagues to watch later, to see how well you did.

STAIC, Speech Evaluation Questionnaire

Also, asked to rate how difficult they found the tasks etc.

Symptom focusing vs. Distraction Task:

SF.

For the next few minutes, I'd like you to try your best to think about each of the ideas on the following pages.

Read each item slowly and silently to yourself. As you read the items, use your imagination and concentration to think the causes, meanings and consequences of the items. Spend a few moments visualising and concentrating on each item, attempting to make sense of and understand the issues raised by each item.

It doesn't matter if you don't get to the end of the list – everyone goes at different speeds and that doesn't matter at all. If you do get to the end of the list then please go back to the beginning and start again.

I'm going to time you for 8 minutes and then I will tell you to stop.

D.

For the next few minutes, try your best to focus your attention on each of the ideas on the following pages. Read each item slowly and silently to yourself. As you read the items, use your imagination and concentration to focus your mind on each experience.

It doesn't matter if you don't get to the end of the list – everyone goes at different speeds and that doesn't matter at all. If you do get to the end of the list then please go back to the beginning and start again.

I'm going to time you for 8 minutes and then I will tell you to stop.

Exercise Task

Use a standard chair with arms (keep testing chair consistent for each site). Chair heights recorded in literature vary, generally 43-45 cm.

Ensure that the chair is not secured (i.e against the wall or mat).

Patient Instructions: "I want you to stand up and sit down 5 times as quickly as you can when I say 'Go'."

o Instruct to stand fully between repetitions of the test and not to touch the back of the chair during each repetition.

- It is OK if the patient does touch the back of the chair, but it is not recommended.

Timing begins at "Go" and stops when the patient's buttocks touch the chair on the fifth repetition.

Provide one practice trial before measurements are recorded. If you are concerned that the patient may fatigue with a practice trial, it is OK to demonstrate to the patient and have the patient do two repetitions to ensure they understand the instructions.

Inability to complete five repetitions without assistance or use of upper extremity support indicates failure of test. (Any modifications should be documented)

Try NOT to talk to the patient during the test (may decrease patient’s speed)

Appendix 13: Symptom focusing vs. distraction task

SF Instructions

For the next few minutes, I'd like you to try your best to think about each of the ideas on the following pages.

Read each item slowly and silently to yourself. As you read the items, use your imagination and concentration to think the causes, meanings and consequences of the items. Spend a few moments visualising and concentrating on each item, attempting to make sense of and understand the issues raised by each item.

It doesn't matter if you don't get to the end of the list – everyone goes at different speeds and that doesn't matter at all. If you do get to the end of the list then please go back to the beginning and start again.

I'm going to time you for 8 minutes and then I will tell you to stop.

Think about:

The physical sensations in your body at the moment

Think about:

How awake or tired you are

Think about:

How clearly you are thinking right now

Think about:

Your present feelings of fatigue or energy

Think about:

Your level of concentration right now

Think about:

Sensations in your muscles and joints

Think about:

The level of motivation you feel right now

Think about:

The way you feel

Think about:

Sensations in your throat right now

Think about:

How passive or active you feel

Think about:

The way your body feels right now

Think about:

How weak or strong your body feels right now

Think about:

How quick or slow your thinking is right now

Think about:

How heavy or light your body feels

Think about:

Your physical sensations

Think about:

Sensations in your glands right now

Think about:

Feelings of fogginess or clearness in your brain right now

Think about:

The way you feel inside

Think about:

Feelings in your muscles

D Instructions

For the next few minutes, try your best to focus your attention on each of the ideas on the following pages. Read each item slowly and silently to yourself. As you read the items, use your imagination and concentration to focus your mind on each experience.

It doesn't matter if you don't get to the end of the list – everyone goes at different speeds and that doesn't matter at all. If you do get to the end of the list then please go back to the beginning and start again.

I'm going to time you for 8 minutes and then I will tell you to stop.

Think about:

And imagine a boat slowly crossing the Atlantic

Think about:

The layout of a typical classroom

Think about:

The shape of a large black umbrella

Think about:

The movement of an electric fan on a warm day

Think about:

Raindrops sliding down a windowpane

Think about:

A double-decker bus driving down a street

Think about:

A full moon on a clear night

Think about:

Clouds forming in the sky

Think about:

The layout of the local shopping centre

Think about:

A plane flying overhead

Think about:

Fire darting around a log in a fire-place

Think about:

The expression on the face of the Mona Lisa

Think about:

A clown putting on his or her make-up

Think about:

Two birds sitting on a tree branch

Think about:

The shadow of a stop sign

Think about:

The layout of the local post office

Think about:

The structure of a high-rise office building

Think about:

The Eiffel Tower

Think about:

A truckload of watermelons

Appendix 14: Symptom focusing vs. distraction task full analyses

		CFS		Asthma		Healthy control		Result
		Pre	Post	Pre	Post	Pre	Post	2x3x2 RM ANOVA
How happy are you feeling at this moment in time?	Symptom focusing	59.97 (15.70)	55.85 (19.34)	72.38 (18.72)	65.19 (18.31)	71.70 (19.21)	68.03 (14.70)	Within subjects effects: Time: F(1,163) = 2.776, p = .098 Time*group: F(2,163) = .326, p = .723 Time*condition: F(1,163) = 9.514, p = .002* Time*condition*group: F(2,163) = .202, p = .817 Between subjects effects: F(2,163) = 14.853, p = .000* Group*condition: F(2,163) = .494, p = .611
	Distraction	57.25 (14.00)	58.14 (14.79)	64.07 (22.70)	70.08 (24.10)	73.66 (14.49)	75.85 (16.65)	
How sad are you feeling at this moment in time?	Symptom focusing	24.59 (20.47)	32.47 (21.89)	10.13 (10.40)	17.15 (15.68)	14.32 (16.53)	17.95 (17.92)	Within subjects effects: Time: F(1,163) = 7.672, p = .006* Time*group: F(2,163) = 1.483, p = .230
	Distraction	26.21 (19.95)	25.46 (20.40)	9.20 (12.31)	12.77 (13.94)	12.20 (13.19)	9.90 (15.62)	

								Time*condition: F(1,163) = 7.616, p = .006* Time*condition*group: F(2,163) = .336, p = .715 Between subjects effects: F(2,163) = 14.473, p = .000* Group*condition: F(2,163) = .123, p = .885
How anxious are you feeling at this moment in time?	Symptom focusing	27.15 (21.78)	25.21 (19.47)	23.25 (29.62)	22.56 (28.22)	21.70 (21.32)	18.97 (20.01)	Within subjects effects: Time: F(1,163) = 7.216, p = .008* Time*group: F(2,163) = .193, p = .824 Time*condition: F(1,163) = 1.260, p = .263 Time*condition*group: F(2,163) = .346, p = .708 Between subjects effects: F(2,163) = 2.773, p = .065 Group*condition: F(2,163) = .796, p = .453
	Distraction	30.00 (23.11)	27.57 (24.11)	14.53 (14.91)	10.54 (12.01)	22.34 (22.73)	17.95 (21.60)	
How	Symptom	42.29 (24.17)	50.74 (26.37)	14.06 (18.45)	19.75 (14.85)	22.57 (21.42)	27.73 (22.90)	Within subjects effects:

mentally fatigued are you feeling at this moment in time?	focusing							Time: F(1,163) = 14.428, p = .000* Time*group: F(2,163) = 3.046, p = .050* Time*condition: F(1,163) = .447, p = .505 Time*condition*group: F(2,163) = 1.826, p = .164 Between subjects effects: F(2,163) = 29.658, p = .000* Group*condition: F(2,163) = .288, p = .750
	Distraction	50.21(24.38)	55.46 (25.30)	15.13 (15.96)	28.00 (24.25)	27.85 (22.55)	24.66 (21.51)	
How physically fatigued are you feeling at this moment in time?	Symptom focusing	39.79(26.76)	41.85 (27.83)	15.88 (16.31)	24.19 (20.15)	16.24 (19.24)	18.27 (20.29)	Within subjects effects: Time: F(1,165) = .491, p = .485 Time*group: F(2,165) = .207, p = .813 Time*condition: F(1,165) = 7.044, p = .009* Time*condition*group: F(2,165) = 2.737, p = .068 Between subjects effects: F(2,165) = 30.452, p = .000*
	Distraction	49.68 (24.56)	51.29 (25.83)	20.60 (27.91)	13.33 (17.80)	20.76 (22.52)	19.20 (20.52)	

								Group*condition: F(2,165) = .962, p = .384
How much pain are you feeling in your body at this moment in time?	Symptom focusing	27.44 (20.97)	32.24 (24.45)	10.06 (16.83)	11.88 (17.25)	9.00 (11.50)	7.59 (8.65)	Within subjects effects: Time: F(1,163) = 1.052, p = .307 Time*group: F(2,163) = 4.030, p = .020* Time*condition: F(1,163) = 3.621, p = .059 Time*condition*group: F(2,163) = 2.782, p = .065 Between subjects effects: F(2,163) = 39.980, p = .000* Group*condition: F(2,163) =1.566, p = .212
	Distraction	34.75 (28.10)	34.32 (29.64)	2.15 (4.45)	10.53 (22.79)	6.78 (10.31)	5.80 (10.03)	
How concerned are you about your symptoms at this moment in time?	Symptom focusing	29.38 (18.56)	25.62 (17.20)	5.00 (5.77)	11.93 (12.00)	11.97 (20.28)	10.19 (13.54)	Within subjects effects: Time: F(1,111) = .013, p = .911 Time*group: F(2,111) = 1.795, p = .171 Time*condition: F(1,111) = 2.087, p = .151 Time*condition*group: F(2,111) =
	Distraction	37.39 (22.12)	32.41 (24.11)	2.69 (4.09)	8.00 (12.17)	11.85 (20.13)	9.76 (15.86)	

								.278, p = .758 Between subjects effects: F(2,111) = 23.135, p = .000* Group*condition: F(2,111) = 1.334, p = .268

How happy: The repeated measures ANOVA revealed a significant within subjects effect for a time by condition interaction. Post-hoc comparisons were conducted for the whole sample together but splitting for condition given this was an interaction. In the symptom focusing condition, participants were significantly less happy at post task to pre task. There was not a significant difference in the distraction condition.

SF: t(86) = 3.015, p = .003*

D: t(81) = -1.403, p = .164

There was a significant between subjects effect. Here, post-hoc analyses revealed that the CFS group were significantly less happy than both the healthy controls and the asthma group.

How sad: There was a significant effect of time. Post-hoc tests revealed a significant difference from pre- to post-task [t(168) = -2.476, p = .014*]. There was also an effect of time by condition. Post-hoc tests revealed that the SF condition got significantly sadder. The distraction condition was not significant.

SF: T(86) = -3.999, P = .000*

D: t(81) = .652, p = .517

There was a significant between groups effect. Post hoc analyses revealed tha the CFS group were significantly sadder than either of the 2 control groups.

How anxious: Significant within subjects effect of time only. Post-hoc analyses revealed all groups significantly decreased in anxiety [t(168) = 2.906, p = .004*]. No other significant findings emerged.

How mentally fatigued: Significant within subjects effect of time. Post-hoc tests revealed a significant difference, with a general increase in mental fatigue. there was also a significant time by group interaction. The planned post-hoc tests revealed that the CFS group and asthma increased significantly in fatigue but the healthy controls did not. There was also a between subjects effect. The CFS group were significantly more mentally fatigued than either the asthma or the healthy control group.

How physically fatigued: significant within subjects effect of time by condition interaction. Post-hoc analyses revealed that at SF there was a significant increase in physical fatigue but no difference in the distraction condition.

SF: t(86) = -2.077, p = .041*

D: t(81) = .894, p = .374

There was also a significant between group difference. The post-hoc tests showed that the CFS group were significantly more physically fatigued than either of the 2 control groups.

How much pain: there was a significant within subjects' effect of time by group interaction. The post-hoc tests revealed that the CFS group increased significantly in levels of pain, but the other two groups did not. The only other significant finding was a between subjects effect. The CFS group reported significantly more pain than the control groups.

How concerned: The only significant finding here was the between groups difference. The CFS group were significantly more concerned than both the healthy controls and the asthma groups.

Appendix 15: Visual analogue scales (VAS)

How mentally fatigued are you feeling at this moment in time?

0 ——————————————————————— 100

Not at all mentally fatigued — Extremely mentally fatigued

How physically fatigued are you feeling at this moment in time?

0 ——————————————————————— 100

Not at all physically fatigued — Extremely physically fatigued

Please mark with an X on the scale below how you are feeling at this moment in time.

0 ———————————————————————100

Not at all happy — Extremely happy

0 ———————————————————————100

Not at all sad — Extremely sad

0 ———————————————————————100

Not at all anxious — Extremely anxious

How much pain are you feeling in your body at this moment in time?

0 ———————————————————————100

No pain at all — Worst pain ever

How concerned are you feeling about your symptoms at this moment in time?

0 ——————————————————————————— 100

Not at all concerned — Extremely concerned

How well do you think you're going to do on this task? 50% represents average performance.

0 ——————————— 50 ——————————— 100

Not at all well — Extremely well

How difficult do you think you're going to find this task?

0 ——————————————————————————— 100

Not at all difficult — Extremely difficult

How well do you feel you were able to concentrate on the Letter Cancellation Task?

0 ——————————————————————————— 100

Completely unable to concentrate — Can concentrate perfectly

Appendix 16: Letter cancellation task

ID: _____

Time 1: _____

Time 2: _____

PRACTICE

EDBNA F BHGCHDE BGAHECH

DE AHAGFDBHA BCE FHDANH

HNGBGDA FHCEHD FHE AGHG

Cancel H Page 1

CANCEL H

GCHC F ANA BHD FDHEGHEHNEDBNA F BHGCHDE BGAHECHN FGNB A BDCACEGH FH FHDN HBCE BDNEHGNH FGAC FNCHDE AHAGFDBHA BCE FHDANHC FGDHA EHBNCHGDGFNEHB E BDHCACHD FGF AHNE B EHNHNGBGDA FHCEHD FHE AGHGCBNBNCAHD F BNE AH FDGHC

CANCEL H

C F EDBCAHAHGN FDHE BGACBDHENHN FGHE ADCGHNHB FDHA FCHB E B AGHGNHDCN F E F B EGDEHAHNGHNBCHDGFDACA BHC FNHE FHCHDA FHDNCA E BGNDBHNGB EHECGA FH GAD FHNB ECH F ADCHC FHGHNEHB ENGB ADA FDCHE FCDHGANHBGHEDBNHGNE ACHB F

Appendix 17: Borg scale

The rating of my perceived exertion during the exercise is:

Exertion	RPE
No exertion at all	6
Very, Very Light	7
	8
Very Light	9
	10
Fairly Light	11
	12
Somewhat Hard	13
	14
Hard (heavy)	15
	16
Very Hard	17
	18
Very, Very Hard	19
Maximal exertion	20

Appendix 18: State subscale of the STAI

A number of statements which people have used to describe themselves are given below. Read each statement and then tick the appropriate box to the right of the statement to indicate how you feel right now, that is, at this moment. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

	Not at all	Somewhat	Moderately so	Very much so
1. I feel calm	☐	☐	☐	☐
2. I feel secure	☐	☐	☐	☐
3. I am tense	☐	☐	☐	☐
4. I feel strained	☐	☐	☐	☐
5. I feel at ease	☐	☐	☐	☐
6. I feel upset	☐	☐	☐	☐
7. I am presently worrying over possible misfortunes	☐	☐	☐	☐
8. I feel satisfied	☐	☐	☐	☐
9. I feel frightened	☐	☐	☐	☐
10. I feel comfortable	☐	☐	☐	☐
11. I feel self-confident	☐	☐	☐	☐
12. I feel nervous	☐	☐	☐	☐
13. I am jittery	☐	☐	☐	☐
14. I feel indecisive	☐	☐	☐	☐
15. I am relaxed	☐	☐	☐	☐
16. I feel content	☐	☐	☐	☐
17. I am worried	☐	☐	☐	☐
18. I feel confused	☐	☐	☐	☐
19. I feel steady	☐	☐	☐	☐
20. I feel pleasant	☐	☐	☐	☐

Appendix 19: Speech evaluation questionnaire

Speech Evaluation Questionnaire

Please rate how you think you came across in the presentation: put a cross (X) at the point on the scale that best describes how you came across.

Friendly

0--------1--------2---------3---------4---------5---------6---------7---------8---------9---------10

Not at all friendly — Extremely friendly

Awkward

0--------1--------2---------3---------4---------5---------6---------7---------8---------9---------10

Not at all awkward — Extremely awkward

Relaxed

0--------1--------2---------3---------4---------5---------6---------7---------8---------9---------10

Not at all relaxed — Extremely relaxed

Embarrassed

0--------1--------2---------3---------4---------5---------6---------7---------8---------9---------10

Not at all Embarrassed — Extremely embarrassed

Attractive

0--------1---------2---------3--------4---------5---------6---------7---------8---------9---------10

Not at all attractive — Extremely attractive

Nervous

0--------1--------2---------3---------4---------5---------6---------7---------8---------9---------10

Not at all nervous — Extremely nervous

Easy to understand

0--------1--------2---------3---------4---------5---------6---------7---------8---------9--------10

Not at all easy to understand — Extremely easy to understand

Blushing

0--------1--------2---------3---------4---------5---------6---------7---------8---------9---------10

Not at all — Extremely

Interesting

0--------1--------2---------3---------4---------5---------6---------7---------8---------9---------10

Not at all Interesting — Extremely interesting

Stuttered or stammered

0--------1--------2---------3---------4---------5---------6---------7---------8---------9---------10

Not at all — Extremely

Confident

0--------1--------2---------3---------4---------5---------6---------7---------8---------9---------10

Not at all confident — Extremely confident

Left gaps in speech

0--------1--------2---------3---------4---------5---------6---------7---------8---------9---------10

Not at all — Extremely

Funny

0--------1--------2---------3---------4---------5---------6---------7---------8---------9---------10

Not at all Funny — Extremely funny

Hands shaking

0--------1--------2---------3---------4---------5---------6---------7---------8---------9---------10

Not at all — Extremely

Uncomfortable

0--------1--------2---------3---------4---------5---------6---------7---------8---------9---------10

Not at all uncomfortable Extremely uncomfortable

Clear voice

0--------1--------2---------3---------4---------5---------6---------7---------8---------9---------10

Not at all Extremely

Avoided looking at camera

0--------1--------2---------3---------4---------5---------6---------7---------8---------9---------10

Not at all Extremely

Appendix 20: Correlations between objective and perceived performance on the letter cancellation task

		CFS	Asthma	Healthy Control
	Time taken on time 1 and time taken on trial 2	Pearson's r = .930 p = .000*	Pearson's r = .924 p = .000*	Pearson's r = .849 p = .000*
Pre-task VAS	Time taken and how well do you think you'll do	Pearson's r = -.123 p = .340	Pearson's r = .065 p = .727	Pearson's r = .253 p = .025*
	Time taken and how difficult do you think you'll find the task	Pearson's r = .191 p = .136	Pearson's r = -.114 p = .541	Pearson's r = -.084 p = .466
	Time taken and how well do you feel you'll be able to concentrate on this task	Pearson's r = -.151 p = .242	Pearson's r = .341 p = .070	Pearson's r = -.060 p = .603
	Time taken and how anxious do you feel at this moment in time	Pearson's r = .173 p = .179	Pearson's r = -.008 p = .968	Pearson's r = .031 p = .789
Post-task VAS	Time taken and how well do you think you did	Pearson's r = .079 p = .540	Pearson's r = .178 p = .356	Pearson's r = .146 p = .201
	Time taken and how difficult did you find the task	Pearson's r = .208 p = .105	Pearson's r = -.092 p = .637	Pearson's r = .095 p = .408
	Time taken and how well do you feel you were able to concentrate on this task	Pearson's r = -.088 p = .494	Pearson's r = .100 p = .594	Pearson's r = .016 p = .889
	Time taken and how anxious do you feel at this moment in time	Pearson's r = .138 p = .285	Pearson's r = .039 p = .834	Pearson's r = .047 p = .681

Parent VAS	Time taken and how well do you think your child will do on this task	Pearson's r = .044 p = .739	Pearson's r = .139 p = .517	Pearson's r = .008 p = .951
	Time taken and how difficult do you think your child will find this task	Pearson's r = .214 p = .103	Pearson's r = -.181 p = .396	Pearson's r = .146 p = .265
	Time taken and how well do you feel your child will be able to concentrate on this task	Pearson's r = -.140 p = .292	Pearson's r = .287 p = .174	Pearson's r = -.077 p = .561
	Time taken and how anxious does your child feel at this moment in time	Pearson's r = .160 p = .232	Pearson's r = -.006 p = .979	Pearson's r = .123 p = .351

Appendix 21: Correlations between number of errors made and VAS for the letter cancellation task

		CFS	Asthma	Healthy Control
	Errors made on trial 1 and errors made on trial 2	Pearson's r = .700 p = .000*	Pearson's r = .664 p = .000*	Pearson's r = .271 p = .016*
Pre-task VAS	Errors made and how well do you think you'll do	Pearson's r = -.024 p = .855	Pearson's r = .316 p = .083	Pearson's r = .253 p = .025*
	Errors made and how difficult do you think you'll find the task	Pearson's r = .170 p = .186	Pearson's r = .426 p = .017*	Pearson's r = -.084 p = .466
	Errors made and how well do you feel you'll be able to concentrate on this task	Pearson's r = -.049 p = .704	Pearson's r = .190 p = .324	Pearson's r = -.060 p = .603
	Errors made and how anxious do you feel at this moment in time	Pearson's r = .199 p = .122	Pearson's r = .146 p = .450	Pearson's r = .031 p = .789
Post-task VAS	Errors made and how well do you think you did	Pearson's r = .019 p = .881	Pearson's r = .148 p = .443	Pearson's r = .146 p = .201
	Errors made and how difficult did you find the task	Pearson's r = .055 p = .672	Pearson's r = -.404 p = .030*	Pearson's r = -.095 p = .408
	Errors made and how well do you feel you were able to concentrate on this task	Pearson's r = -.141p = .275	Pearson's r = .285 p = .121	Pearson's r = .016 p = .889
	Errors made and how anxious do you feel at this moment in time	Pearson's r = .141 p = .276	Pearson's r = -.038 p = .839	Pearson's r = .047 p = .681
	Errors made and how well do you think your child will do on this task	Pearson's r = -.287 p = .027*	Pearson's r = .149 p = .487	Pearson's r = .008 p = .951
	Errors made and how difficult do you think your child will find this task	Pearson's r = .107p = .421	Pearson's r = -.199 p = .352	Pearson's r = .146 p = .265

Parent VAS	Errors made and how well do you feel your child will be able to concentrate on this task	Pearson's r = -.272 p = .037*	Pearson's r = .230 p = .280	Pearson's r = -.077 p = .561
	Errors made and how anxious does your child feel at this moment in time	Pearson's r = .079 p = .554	Pearson's r = .099 p = .644	Pearson's r = .123 p = .351

Appendix 22: Parent and child correlations for the letter cancellation task

	Chronic Fatigue Syndrome	Asthma	Healthy Controls
How well do you think you'll do on the task?	Pearson's r = -.042, p = .752	Pearson's r = .730, p = .000*	Pearson's r = .057, p = .667
How difficult do you think you'll find the task?	Pearson's r = .255, p = .051	Pearson's r = -.171, p = .425	Pearson's r = -.098, p = .456
How mentally fatigued are you at this moment in time?	Pearson's r = 266, p = .042*	Pearson's r = .091, p = .674	Pearson's r = .171, p = .191
How physically fatigued are you at this moment in time?	Pearson's r = .238, .070	Pearson's r = .621, p = .002*	Pearson's r = .338, p = .008*
How well will you be able to concentrate on this task?	Pearson's r = 232, p = .077	Pearson's r = .693, p = .000*	Pearson's r = .166, p = .204
How anxious are you at this moment in time?	Pearson's r = .276, p = .036	Pearson's r = .041, p = .856	Pearson's r = .381, p = .003*

Note: All questions have a parent equivalent

Appendix 23: Correlations between objective and perceived performance on the exercise task

		CFS	Asthma	Healthy Control
	Time taken on time 1 and time taken on trial 2	Pearson's r = .915 p = .000*	Pearson's r = .912 p = .000*	Pearson's r = .902 p = .000*
Pre-task VAS	Time taken and how well do you think you'll do	Pearson's r = -.116 p = .398	Pearson's r = .053 p = .789	Pearson's r = .038 p = .746
	Time taken and how difficult do you think you'll find the task	Pearson's r = .323 p = .016*	Pearson's r = -.002 p = .990	Pearson's r = .078 p = .506
	Time taken and how anxious do you feel at this moment in time	Pearson's r = .362 p = .007*	Pearson's r = .117 p = .555	Pearson's r = .148 p = .205
Post-task VAS	Time taken and how well do you think you did	Pearson's r = -.129 p = .349	Pearson's r = .443 p = .018*	Pearson's r = .025 p = .834
	Time taken and how difficult did you find the task	Pearson's r = .412 p = .002*	Pearson's r = .049 p = .806	Pearson's r = .069 p = .559
	Time taken and how anxious do you feel at this moment in time	Pearson's r = .361 p = .007*	Pearson's r = .059 p = .767	Pearson's r = .187 p = .108
Parent VAS	Time taken and how well do you think your child will do on this task	Pearson's r = .340 p = .013*	Pearson's r = -.054 p = .810	Pearson's r = -.255 p = .055
	Time taken and how difficult do you think your child will find this task	Pearson's r = .374 p = .006*	Pearson's r = .324 p = .142	Pearson's r = .282 p = .034*
	Time taken and how anxious does your child feel at this moment in time	Pearson's r = .439 p = .001*	Pearson's r = .088 p = .696	Pearson's r = .358 p = .006*

Appendix 24: Exercise task performance (time taken) and correlations with clinical questionnaire measures

	Chronic Fatigue Syndrome	Asthma	Healthy Controls
Physical functioning	Pearson r = .415, p = .001*	Pearson r = .079, p = .673	Pearson r = -.309, p = .007*
Impairment (WASA)	Pearson r = .293, p = .028*	Pearson r = .338, p = .063	Pearson r = -.080, p = .497
Self oriented perfectionism	Pearson r = .183, p = .177	Pearson r = .454, p = .010*	Pearson r = -.215, p = .066
Socially prescribed perfectionism	Pearson r = -.144, p = .288	Pearson r = .314, p = .086	Pearson r = -.187, p = .108
Fear avoidance	Pearson r = .081, p = .552	Pearson r = .081, p = .664	###
Catastrophising	Pearson r = .038, p = .779	Pearson r = .257, p = .167	###
Damage	Pearson r = .021, p = .877	Pearson r = .189, p = .308	###
Embarrassment avoidance	Pearson r = .158, p = .243	Pearson r = .262, p = .154	###
Symptom focusing	Pearson r = .099, p = .467	Pearson r = .010, p = .959	###
All or nothing behaviour	Pearson r = -.102, p = .233	Pearson r = .040, p = .830	###
Avoidance resting behaviour	Pearson r = .171, p = .208	Pearson r = .110, p = .557	###
State anxiety	Pearson r = .125, p = .361	Pearson r = .344, p = .058	Pearson r = .111, p = .348
Trait anxiety	Pearson r = .085, p = .536	Pearson r = .168, p = .367	Pearson r = -.011, p = .928
Depression inventory	Pearson r = .181, p = .182	Pearson r = .102, p = .583	Pearson r = .127, p = .278

Appendix 25: Parent VAS results tables for the task session

Letter cancellation task

	Chronic Fatigue Syndrome	Asthma	Healthy Controls	Results
	Mean (SD)	Mean (SD)	Mean (SD)	
How well do you think your child is going to do on this task?	76.22 (20.81)a	78.88 (31.81)ab	84.00 (14.92)b	F(2,140) = 2.085, p = .071
How difficult do you think your child is going to find it?	29.37 (26.07)	14.46 (26.79)a	11.28 (12.58)a	F(2,140) = 10.933, p = .000*
How mentally fatigued is your child feeling at this moment in time?	57.03 (25.62)	16.17 (14.36)a	20.43 (18.86)a	F(2,140) = 54.738, p = .000*
How physically fatigued is your child feeling at this moment in time?	56.58 (24.06)	13.08 (11.38)a	15.85 (17.24)a	F(2,140) = 77.486, p = .000*
How well do you feel your child will be able to concentrate on this task?	68.93 (21.24)	85.54 (22.81)a	81.68 (22.99)a	F(2,140) = 6.975, p = .001*
How anxious is your child at this moment in time?	30.81 (24.34)b	25.00 (23.32)ab	13.33 (15.15)a	F(2,140) = 10.686, p = .000*

Social performance task

	Chronic Fatigue Syndrome	Asthma	Healthy Controls	Results
	Mean (SD)	Mean (SD)	Mean (SD)	
How well do you think your child is going to do on this task?	64.80 (24.15)	73.71 (19.55)a	78.53 (19.24)a	F(2,134) = 6.006, p = .003*
How difficult do you think your child is going to find it?	43.80 (26.38)a	41.24 (34.57)a	25.58 (25.97)	F(2,134) = 6.868, p = .001*
How mentally fatigued is your child feeling at this moment in time?	57.41 (21.26)	29.10 (26.66)a	17.97 (17.90)a	F(2,134) = 53.371, p = .000*
How physically fatigued is your child feeling at this moment in time?	55.61 (25.35)	10.86 (10.74)a	13.03 (18.89)a	F(2,134) = 70.424, p = .000*
How anxious is your child at this moment in time?	39.75 (24.64)b	35.67 (28.70)ab	24.50 (23.44)a	F(2,134) = 5.695, p = .004*

Exercise task

	Chronic Fatigue Syndrome	Asthma	Healthy Controls	Results
	Mean (SD)	Mean (SD)	Mean (SD)	
How well do you think your child is going to do on this task?	55.91 (26.44)	90.68 (9.49)a	87.35 (13.37)a	F(2,130) = 44.862, p = .000*
How difficult do you think your child is going to find it?	46.00 (29.00)	9.59 (12.92)a	10.05 (15.54)a	F(2,129) = 43.833, p = .000*
How mentally fatigued is your child feeling at this moment in time?	54.19 (27.00)	11.82 (12.03)a	10.91 (12.66)a	F(2,129) = 75.869, p = .000*
How physically fatigued is your child feeling at this moment in time?	61.19 (25.16)	20.05 (22.60)a	16.28 (18.53)a	F(2,129) = 62.840, p = .000*
How much pain do you feel your child is in at this moment in time?	36.26 (27.50)	5.18 (6.57)a	6.44 (9.91)a	F(2,129) = 40.763, p = .000*
How anxious is your child at this moment in time?	36.38 (24.87)	20.05 (20.63)a	12.70 (14.46)a	F(2,129) = 19.170, p = .000*

Appendix 26: Cortisol questions

Have you felt ill?	
Taken any medication?	
Ear infection?	
Eye Infection?	
Period?	
Problems in mouth?	

In the last 24 hours...

Time of testing:

Food eaten today and at what time?

If not 2hours pre-testing, washed mouth out with water and noted timings?

What time awoken?

Cough medicine?

Age?

Date seen?

Where tested?

Any arguments/bad news etc? Adverse events?

Any sport? Or exercise?

Mouth ulcers?

When last visited dentist?

Asthma?

Appendix 27: Further analysis description for cortisol chapter

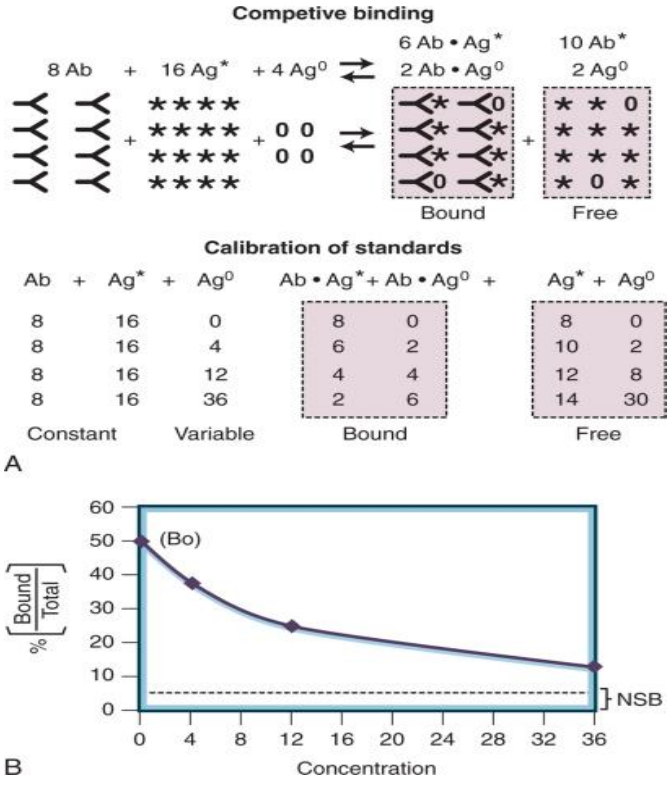
All participant samples were taken to a specialist laboratory at the Royal Bethlem Hospital for analyses having been stored in a freezer at King's College Hospital after task session sampling. Concentrations of cortisol in the saliva are much lower than those of general chemistry analytes and specialised laboratory techniques are necessary to measure these low concentrations. An analyte is the substance going under analysis. There are 3 major types of assays for measuring hormones; immunoassays, chromatography and mass spectrometry. An immunoassay analyser was used in this study, more specifically a competitive immunoassay. The term competitive immunoassay refers to a measurement method in which an antigen (e.g. a hormone like cortisol) in a specimen competes with labelled reagent antigen for a limited number of binding sites on a reagent antibody.

The 3 basic components of a competitive immunoassay are (Price & Newman, 1996):

Antiserum specific for a unique epitope on a hormone or antigen

Labelled antigen that binds to this antiserum

Unlabelled antigen in the specimen or standard that is to be measured (i.e. cortisol collected from participant)



From Klee, G. (Book Chapter: Laboratory techniques for recognition of endocrine disorders). The figure illustrates the concepts of a competitive immunoassay. Here, 8 units of antibody react with 16 units of labelled antigen and 4 units of participant antigen. Given the proportions, one would predict, at equilibrium, 6 units of labelled and 2 units of participant antigen are bound to the limited supply of antibody (8 units in total). The antigen bound to the antibody is separated from the liquid antigen by any of several methods, and the amount of labelled antigen in the bound portion is quantified. The assay is calibrated by measuring standards with known concentrations and cross-plotting the signal versus the concentration of the standards to generate a dose-response curve. As the concentration increases, the signal decreases exponentially i.e., the higher the concentration of the unlabelled antigen (participant sample), the lower the amount of labelled antigen that binds to the limited amount of antiserum.

Salivary cortisol concentrations were determined using the chemiluminescence assay of "Immulite". This chemiluminescence is used to label the antigen. The Immulite system used was developed by Diagnostic Products Corporation (DPC) and is a continuous, random-access automated immunoassay analyser designed around a proprietary assay tube called a test unit which allows for thorough and efficient washing of an integral antibody or antigen-coated bead by rapidly spinning the tube on its vertical axis.

This equipment is in the laboratory at the Bethlem Royal Hospital and the team there load samples in bar-coded sample cups into the loading chain of the immulite instrument followed by up to 5 bar-coded, assay-specific test units in any order. All subsequent steps are performed automatically by the system. The immulite dispenses the sample, selects and dispenses the reagent, incubates, separates bound from free antigens/portions, dispenses substrate and reads signal all automatically as follows (taken from Babson, 2005):

Sample and alkaline phosphate-labelled reagent are added to a test unit

The reaction is incubated for 30 minutes at 37°C and shaken every 10 seconds

The bead is washed

Chemiluminescent substrate is added

The reaction is incubated for 10 minutes at 37°C

The luminescence is read

Appendix 28: Cortisol correlations with clinical questionnaire measures

	Area under the curve ground (nmol/l)			Area under the curve increase (nmol/l)		
	CFS	Asthma	Healthy controls	CFS	Asthma	Healthy controls
Baseline HR	Pearson r = .315, p = .061	Pearson r = .060, p = .787	Pearson r = .130, p = .307	Pearson r = .025, p = .884	Pearson r = .115, p = .600	Pearson r = .121, p = .342
Fatigue (CFQ)	Pearson r = .123, p = .426	Pearson r = -.033, p = .882	Pearson r = .094, p = .447	Pearson r = -.166, p = .283	Pearson r = -.052, p = .814	Pearson r = -.013, p = .917
Physical functioning (SF36)	Pearson r = -.194, p = .208	Pearson r = .290, p = .179	Pearson r = .044, p = .723	Pearson r = .040, p = .795	Pearson r = -.065, p = .767	Pearson r = .044, p = .724
Self-oriented perfectionism	Pearson r = -.095, p = .540	Pearson r = -.286, p = .186	Pearson r = -.005, p = .968	Pearson r = -.001, p = .995	Pearson r = -.087, p = .694	Pearson r = .207, p = .092
Socially prescribed perfectionism	Pearson r = .026, p = .869	Pearson r = -.311, p = .149	Pearson r = .026, p = .838	Pearson r = .006, p = .971	Pearson r = -.055, p = .802	Pearson r = .090, p = .470
Anxiety (SPAI-c)	Pearson r = .123, p = .448	Pearson r = -.101, p = .672	Pearson r = .277, p = .023*	Pearson r = .138, p = .396	Pearson r = .055, p = .816	Pearson r = .105, p = .399
Depression (CDI)	Pearson r = .198, p = .198	Pearson r = -.196, p = .370	Pearson r = .090, p = .468	Pearson r = -.068, p = .659	Pearson r = -.051, p = .817	Pearson r = -.048, p = .700
State STAI	Pearson r = -.231, p = .302	Pearson r = .053, p = .834	Pearson r = .029, p = .855	Pearson r = -.128, p = .572	Pearson r = -.200, p = .426	Pearson r = .208, p = .181

Appendix 29: Correlations of time 1 measures repeated at time 2

	Chronic Fatigue Syndrome Mean (SD)		Healthy Controls Mean (SD)	
	Time 1	Time 2	Time 1	Time 2
Fatigue (CFQ Binary)	8.21 (3.07)	7.45 (3.40)	1.81 (1.72)	1.28 (2.10)
Fatigue (CFQ Total)	23.09 (6.16)	21.55 (7.79)	10.46 (3.76)	10.55 (3.80)
Physical functioning (SF36)	49.84 (25.90)	55.07 (26.68)	90.38 (16.99)	93.55 (14.53)
School and social adjustment	24.42 (7.79)	21.06 (9.69)	1.09 (3.10)	.435 (1.40)
Self-oriented perfectionism	38.64 (4.10)	37.82 (4.64)	38.47 (3.64)	39.20 (3.96)
Socially-prescribed perfectionism	26.42 (6.87)	26.69 (6.59)	28.41 (6.51)	27.51 (6.06)
Insomnia scale	22.43 (9.49)	18.48 (10.66)	8.65 (8.80)	6.74 (7.23)
Fear avoidance subscale of the CBRQ	14.74 (3.61)	14.66 (4.07)	###	###
Catastrophising subscale of the CBRQ	7.82 (3.15)	6.45 (4.03)	###	###
Damage subscale of the CBRQ	10.02 (3.32)	9.05 (3.87)	###	###
Embarrassment avoidance subscale of the CBRQ	8.86 (4.97)	7.96 (6.05)	###	###
Symptom focusing subscale of the	11.61 (5.03)	9.88 (5.45)	###	###

CBRQ				
Avoidance resting behaviour subscale of the CBRQ	14.32 (5.30)	12.11 (6.17)	###	###
All or nothing behaviour subscale of the CBRQ	9.17 (4.56)	8.81 (5.00)	###	###
Beliefs about emotions	32.87 (14.26)	31.71 (12.35)	31.55 (14.51)	29.30 (12.80)
State scale of the STAI	43.94 (11.80)	41.77 (11.51)	34.62 (11.44)	32.00 (11.42)
Trait scale of the STAI	46.38 (10.75)	46.04 (12.59)	37.49 (11.19)	33.74 (11.37)
Depression (CDI)	14.34 (7.72)	13.80 (8.87)	5.64 (5.18)	4.86 (5.92)
Anxiety (SPAI-c)	13.06 (9.86)	14.82 (12.09)	10.06 (7.42)	8.66 (8.87)